

THORACOSCOPIC VIEW OF A PNEUMOTHORAX OF SIX MONTHS' DURATION. DRAWING, MADE AT THE TIME OF OPERATION, ILLUSTRATES THE VARIETY OF ADHESIONS PRESENT IN THIS CASE. PAGE 99.

- a. Central tendon of the diaphragm.
- b. Inferior vena cava.
- c. Broad band adhesion extending between the lower lobe of the lung, the diaphragm and the pericardium. (No technical importance.)
- d. A diffuse adhesion containing lung pigment close to the chest wall. (Inoperable type.)
- e. Vascular band adhesion. (Very appropriate for operation.)
- f. Arachnoid adhesion extending between the upper and lower lung lobes. (No technical importance.)
- g. Two string adhesions. (No technical importance.)
- h. Cone-shaped adhesion containing the prolongation of a cavity; lung tissue extends to the chest wall—must be excised around the chest wall attachment.
- i. Cord adhesion. (Technical importance.)
- j. Spindle adhesion containing lung tissue and blood channels well up to its narrowest diameter, but must be severed at the chest wall attachment.
- k-l. Right and left innominate veins.
- m. Ascending aorta.
- n. Superior vena cava.
- o. Phrenic nerve.
- p. Relatively vascular band adhesion extending between the lower lobe of the lung and the pericardium. (The fissure between the upper and middle lobes of the lung was not visualized because of pleuritic thickening and obliteration of the fissure. The upper and middle lobes are well collapsed. The adhesions at (h, i and j) were responsible for an unsatisfactory pneumothorax. Their severance was followed by prompt closure of the cavity.)

INTERNATIONAL CLINICS

A Quarterly

OF

ILLUSTRATED CLINICAL LECTURES AND
ESPECIALLY PREPARED ORIGINAL ARTICLES

ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PÆDIATRICS, OBSTET-
RICS, GYNÆCOLOGY, ORTHOPÆDICS, PATHOLOGY, DERMA-
TOLOGY, OPHTHALMOLOGY, OTOTOLOGY, RHINOLOGY,
LARYNGOLOGY, HYGIENE, AND OTHER
TOPICS OF INTEREST

BY LEADING MEMBERS OF THE MEDICAL PROFESSION
THROUGHOUT THE WORLD

Edited by

LOUIS HAMMAN, M.D.

Visiting Physician, Johns Hopkins Hospital, Baltimore, Md.

With the Collaboration of

FRANCIS GILMAN BLAKE, M.D.

Yale University, New Haven, Conn.

VERNON C. DAVID, M.D.

Rush Medical College, Chicago, Ill.

DEAN LEWIS, M.D.

Johns Hopkins Hospital, Baltimore, Md.

JOHN W. McNEE, M.D.

University College Hospital, London, Eng.

JOHN H. MUSSER, M.D.

Tulane University, New Orleans, La.

WALTER W. PALMER, M.D.

Columbia University, New York, N. Y.

PASTEUR VALLERY—RADOT, M.D.

University of Paris, Paris, France

ARTHUR L. BLOOMFIELD, M.D.

Stanford University, San Francisco, Cal.

CAMPBELL P. HOWARD, M.D.

McGill University, Montreal, Canada

W. McKIM MARRIOTT, M.D.

Washington University, St. Louis, Mo.

GEORGE RICHARDS MINOT, M.D.

Harvard University, Boston, Mass.

CHARLES C. NORRIS, M.D.

University of Pennsylvania, Phila., Pa.

E. REHN, M.D.

University of Freiburg, Germany

RUSSELL M. WILDER, M.D.

The Mayo Foundation, Rochester, Minn.

VOLUME II. FORTY-FOURTH SERIES, 1934

PHILADELPHIA MONTREAL LONDON
J. B. LIPPINCOTT COMPANY

COPYRIGHT, 1934

BY

J. B. LIPPINCOTT COMPANY

PRINTED IN THE UNITED STATES OF AMERICA

CONTRIBUTORS TO VOLUME II

(FORTY-FOURTH SERIES)

	PAGE
BAKER, BENJAMIN M., JR., M.D., Instructor in Medicine, Johns Hopkins University School of Medicine: Assistant Visiting Physician, Johns Hopkins Hospital, Baltimore, Maryland.....	167
COHN, ISIDORE, M.D., F.A.C.S., Associate Senior Surgeon, Touro Infirmary: Professor of Surgery, Graduate School of Medicine, Tulane University, New Orleans, Louisiana.....	225
EASTMAN, NICHOLSON J., M.D., Professor of Obstetrics and Gynecology, Peiping Union Medical College, Peiping, China.....	236
EITEL, HERMANN, M.D., Assistant in the Surgical Clinic, University of Freiburg, Germany.....	66
GOLDBLOOM, A. ALLEN, M.D., Adjunct Physician, Beth Israel Hospital, New York City, New York.....	133
GOLDSTEIN, HYMAN I., M.D., Fellow of the American Editors' and Authors' Association: Associate of the American College of Physicians, Camden, New Jersey.....	43
HELD, I. W., M.D., Attending Physician at Beth Israel Hospital, New York City, New York.....	133
LOESER, ARNOLD, M.D., Assistant in the Institute, University of Freiburg, Germany	66
LONGCOPE, WARFIELD T., M.D., Professor of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.....	1
LOVETT, THELMA, M.A., Philadelphia, Pennsylvania.....	16
MCBRIDE, EARL D., M.D., F.A.C.S., Oklahoma City, Oklahoma.....	206
MATSON, RALPH C., M.D., F.A.C.S., Associate Clinical Professor of Medicine, University of Oregon Medical School, Portland, Oregon; Director, Department of Surgery, Portland Open Air Sanatorium, Portland, Oregon..	99
MATSON, RAY W., M.D., Assistant Clinical Professor of Medicine, University of Oregon Medical School, Portland, Oregon; Co-Medical Director, Portland Open Air Sanatorium, Portland, Oregon.....	99
PAYNE, R. L., M.D., F.A.C.S., Surgical Staff, St. Vincent's and Norfolk Protestant Hospitals, Norfolk, Virginia.....	188
REHN, E., M.D., Professor of Surgery, University of Freiburg, Germany....	57

RIENHOFF, WILLIAM FRANCIS, JR., M.D., Associate in Surgery, Johns Hopkins University School of Medicine; Assistant Visiting Surgeon, Johns Hopkins Hospital, Baltimore, Maryland.....	167
SCHNEIDER, ERICH, M.D., Privadozent, University of Freiburg, Germany.....	87
WHITEHEAD, R. C., M.D., Medical Staff, St. Vincent's and Norfolk Protestant Hospitals, Norfolk, Virginia.....	188
WILKINS, LAWSON, M.D., Instructor in Pediatrics, Johns Hopkins University School of Medicine; Visiting Pediatrician, Johns Hopkins Hospital, Baltimore, Maryland.....	266

CONTENTS OF VOLUME II

(FORTY-FOURTH SERIES)

MEDICINE

	PAGE
GENERALIZED EDEMA ASSOCIATED WITH DISEASE OF THE GASTRO-INTESTINAL TRACT. BY WARFIELD T. LONGCORE, M.D., Baltimore, Maryland.....	1
THE PATHOGENESIS OF ANTERIOR POLIOMYELITIS. A REVIEW. BY THELMA LOVETT, M.A., Philadelphia, Pennsylvania.....	16
HEREDOFAMILIAL ANGIOMATOSIS (TELANGIECTASIA) WITH RECURRENT HEMORRHAGES. BY HYMAN I. GOLDSTEIN, M.D., Camden, New Jersey.....	43

SURGERY

OPERATIVE SHOCK. BY E. REHN, M.D., Freiburg, Germany.....	57
THE ANTERIOR LOBE OF THE PITUITARY GLAND, THE THYROID GLAND AND THE CARBOHYDRATE METABOLISM OF THE LIVER. BY HERMANN EITEL, M.D., and ARNOLD LOESER, M.D., Freiburg, Germany	66
CONCERNING THE BROADENING OF THE INDICATIONS FOR OPERATION IN EXOPHTHALMIC GOITER THROUGH THE RECOGNITION AT THE BEDSIDE OF A SECONDARY THYROGENIC INJURY TO THE LIVER. BY EMICH SCHNEIDER, M.D., Freiburg, Germany.....	87
OPERATIVE COLLAPSE THERAPY IN THE TREATMENT OF PULMONARY TUBERCULOSIS. BY RALPH C. MATSON, M.D., and RAY C. MATSON, M.D., Portland, Oregon.....	99
INDICATIONS FOR SURGICAL TREATMENT OF PEPTIC ULCER; METHODS; POSTOPERATIVE COMPLICATIONS AND SEQUELAE AND THEIR TREATMENT. BY I. W. HELD, M.D., and A. ALLEN GOLDBLOOM, M.D., New York City, New York.....	133
THE MEDICAL AND SURGICAL ASPECTS OF PEPTIC ULCER. BY WILLIAM FRANCIS RIENHOFF, JR., M.D., and BENJAMIN M. BAKER, JR., M.D., Baltimore, Maryland.....	167
PURPURA HEMORRHAGICA. BY L. R. PAYNE, M.D., and R. C. WHITEHEAD, M.D., Norfolk, Virginia.....	188
ESTIMATING THE EXTENT OF DISABILITY. BY EARL D. McBRIDE, M.D., Oklahoma City, Oklahoma.....	206
THE CRIPPLED HAND. BY ISIDORE COHN, M.D., New Orleans, Louisiana	225

RECENT PROGRESS IN OBSTETRICS AND PEDIATRICS

	PAGE
PROGRESS IN OBSTETRICS. THE TOXEMIAS OF LATER PREG- NANCY. BY NICHOLSON J. EASTMAN, PEIPING, CHINA.....	236
PROGRESS IN PEDIATRICS. IMMUNIZATION AGAINST THE CON- TAGIOUS DISEASES OF CHILDHOOD. 1. DIPHTHERIA. 2. SCARLET FEVER. BY LAWSON WILKINS, M.D., Baltimore, Maryland	286

LIST OF ILLUSTRATIONS TO VOLUME II

(FORTY-FOURTH SERIES)

COLORED PLATE

Thoracoscopic view of a pneumothorax of six months duration.....	
	<i>Frontispiece</i> , page 90

PLATES, FIGURES, GRAPHS, AND CHARTS

	IN OR FACING PAGE
Showing the variations in the total protein and total albumen globulin of the plasma (Chart Case 1).....	8
Liver of a normal guinea pig stained by the Best Method (Fig. 1).....	72
Normal thyroid gland of a guinea pig (Fig. 2).....	72
Thyroid gland of a guinea pig injected with 2.5 mg. of thyrotropic substance of the anterior lobe of the hypophysis (Fig. 3).....	73
Impressive epithelial proliferation, deformation and diminution of the lumen of the acini by the proliferated epithelium (Fig. 4).....	73
A thyroid gland after the injection of 7.5 mg. of anterior lobe of the hypophysis (Fig. 5).....	74
The thyroid gland of a guinea pig after the injection of 12.5 mg. of the anterior lobe of the hypophysis (Fig. 6).....	74
Liver after injection of 12.5 mg. of anterior lobe stained by the Best Method (Fig. 7).....	75
The thyroid gland of a guinea pig after the injection of 17.5 mg. of anterior lobe of the hypophysis (Fig. 8).....	75
The thyroid gland of a guinea pig after the injection of 27.5 mg. of anterior lobe of the hypophysis (Fig. 9).....	76
Liver after the injection of 27.5 mg. of anterior lobe of the hypophysis (Fig. 10).....	76
Thyroid gland of a guinea pig two hours after one injection of 2.5 mg. of anterior lobe substance (Fig. 11).....	77
Electrocardiogram of a normal animal (Fig. 12A) Electrocardiogram of an animal treated for twenty days (Fig. 12B).....	77
Thyroid gland of a guinea pig after the injection of 32.5 mg. of anterior lobe substance of the hypophysis (Fig. 13).....	80
Liver after the injection of 32.5 mg. of anterior lobe substance (Fig. 14)...	80

	IN OR FACING PAGE
Thyroid gland of a guinea pig after 2.5 mg. of anterior lobe substance (Fig. 15)	81
Liver after the injection of 32.5 mg. of anterior lobe substance (Fig. 16)...	81
Remaining thyroid gland rests in a thyroidectomized animal (Fig. 17)	84
The thyroid gland of a guinea pig treated for seven days with boiled thyro-tropic substance (Fig. 18)	84
Fibrocaceous cavernous tuberculosis right upper lobe with fresh bronchogenic extension lower lobe left lung (Fig. 1)	100
Same case as Figure 1 approximately six months later (Fig. 2)	100
Same case as Figures 1 and 2. Two and one-half years later (Fig. 3)	100
Thoracic Hammock for Increasing Chest Wall Collapse and Preventing Scoliosis (Fig. 4)	119
Authors' Surgical Approach to the Phrenic Nerve (Fig. 5)	121
Evaluation of extent of disability (Chart 1)	211
Evaluation of extent of disability in the hand or arm (Chart 2)	212
Evaluation of extent of disability in foot or leg (Chart 3)	213
Evaluation of extent of disability in the eye (Chart 4)	214
Estimating the extent of disability (Fig. 1)	217
Some of the duties of the hand and arm (Fig. 2)	218
Reaching, touching and grasping (Fig. 2)	219
Some duties of the leg (Fig. 3)	219
Some duties of the leg (Fig. 4)	220
Basis of Evaluation (Fig. 4)	221
Final result in ankylosis of the elbow (Fig. 5)	222
The shoulders and elbows form a hoisting device (Fig. 6)	222
In the normal elbow action the fulcrum is at the elbow joint (Fig. 7)	222

Medicine

GENERALIZED EDEMA ASSOCIATED WITH DISEASE OF THE GASTRO- INTESTINAL TRACT*

By WARFIELD T. LONGCOPE, M.D.

Professor of Medicine, Johns Hopkins University, Baltimore, Maryland

THE two cases that form the subject of this report illustrate in a remarkable manner one way in which extensive generalized edema may arise; and show how promptly the edema may be relieved by simple therapeutic measures.

The factors that are supposed to operate in the formation of edema are four: first increased permeability of the capillary walls; secondly increase in intracapillary pressure; thirdly quantitative and qualitative changes in the electrolytes of the blood plasma; and fourthly reduction in colloid osmotic pressure of the blood plasma due to decrease in the protein content of the blood. All of these forces act in relation to somewhat equivalent conditions in the tissue spaces, and it is largely a disturbance in the balance between the intravascular and extravascular forces that leads to the reversal of the normal exchange of fluids and electrolytes, and that determines the accumulation of fluid, as dropsy, in the tissue spaces or serous sacs. It may be pointed out that, in many instances, two or more of these factors work in combination to produce edema. In congestive heart failure, for instance, where the conditions are usually complicated it is supposed that the capillary wall is injured through anoxaemia, that the intracapillary pressure is increased, and it is known that the plasma proteins are usually reduced in quantity. The dropsy in certain forms of Bright's disease is undoubtedly dependent, principally upon a marked reduction in the protein content of the plasma, but it would be improper to neglect as an adjuvant the part played

* From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital.

by the electrolytes of the plasma in their balanced relation with the electrolytes of the tissue spaces.

It is not possible in this report to present, in any detail, the numerous facts about edema that have been brought to light by recent studies, or to discuss the theories that have been evolved from them in an effort to explain the origin of edema. The general subject is dealt with fully by Van Slyke and Peters,¹ by Elwyn,² by Volhard³ and by Govaerts;⁴ Peters⁵ has discussed in detail the important part which the electrolytes play in the production of edema; Leiter⁶ the origin of nephrotic edema, while Landis⁷ and his coworkers have called attention to the importance of the intracapillary pressure and the colloid osmotic pressure in the exchange of fluids between the tissue spaces and the blood vessels.

Although it is impossible to disregard the complicated processes which predispose to the formation of edema or which exaggerate edema once it is initiated by one or another of the factors mentioned above, yet in this report it is desired to lay especial emphasis on the reduction of plasma proteins in their relation to edema; and to discuss some of the ways, as illustrated by two cases, in which the body loses protein or is deprived of protein in such large amounts that the colloid osmotic pressure of the plasma, through reduction of its proteins, is abnormally decreased.

The most common and obvious way in which the body loses protein is through the kidneys. Epstein⁸ laid stress, many years ago, upon the fact that in the edematous form of Bright's disease, now generally termed nephrosis, the excessive albuminuria was associated with a marked reduction in the protein content and an elevation of the total cholesterol content of the plasma. He considered that the dropsy was the result of the hypoproteinaemia, due to loss of albumen through the kidneys; and showed that when patients were fed diets high in protein the edema subsided. Since then, extensive observations have been made on edema of Bright's disease. They show that when anasarca occurs in the subacute and chronic forms, and in the nephrotic variety it is invariably associated with a reduction in the total protein content of the blood, and particularly in a reduction of the albumen fraction. Van Slyke states that edema is likely to occur in Bright's disease when the total protein of the plasma falls below 5.5 Gm. per cent., or when the albumen

fraction reaches 2.5 Gm. per cent. The loss of protein takes place largely through the kidneys. In some instances, however, a restricted diet, low in protein, may be partly responsible for the hypoproteinaemia or exaggerate it. The height of the intracapillary pressure, and the balance of electrolytes and water between the blood plasma and tissue fluids is also of some importance in precipitating or maintaining the edema in Bright's disease. The anasarca that appears suddenly in the acute form of Bright's disease is not, on the other hand, associated with hypoproteinaemia. It has been ascribed to a different combination of circumstances. The sudden elevation in blood pressure, with consequent increase in capillary pressure; injury to the capillary walls by toxins, and acute dilatation of the heart have all been suggested as conditions that might explain the production of this acute edema.

Although albuminuria is the commonest cause for the loss of protein from the body, there are other ways that are almost as effective, in which the body may lose its protein in excessive amounts. Large and repeated haemorrhages may produce hypoproteinaemia, and, when sufficient fluid is administered, result in edema. This has been demonstrated experimentally by Leiter,⁹ and by Barker and Kirk.¹⁰ They have produced anasarca in dogs by making repeated bleedings, and by replacing the blood withdrawn by an equivalent amount of red blood cells in Lock's solution. Although mild degrees of edema are occasionally seen in patients who have had repeated large haemorrhages, an extensive anasarca from this cause must be exceedingly rare, for the immediate effect of haemorrhage is dehydration. Sinuses that drain large amounts of pus form channels through which the body may lose considerable protein. This may happen in empyaema after operation. Mild grades of edema are not uncommon under these conditions. The edema, however, may not be due exclusively to loss of protein, for such accessory factors as malnutrition and infection must also be taken into consideration. Protein may, further, be lost from the body through the bowel, when inflammatory processes, such as dysentery, affect the intestinal tract.

A second way in which the patient may be deprived of a necessary supply of protein is through the inability of the cells of the body to synthesize plasma protein from the products of normal diges-

and contained dark blood. At the onset there was some abdominal pain, and he was greatly troubled by eructations of gas. There was no fever, no chills, no night sweats. Three months ago, noticed his ankles and feet were swollen. The swelling has increased constantly since then. Lately he has had some difficulty in urination. Amount of urine is decreased; no nocturia or hematuria. Six days ago his left arm began to swell, and he has grown progressively worse and weaker. Two months ago, he spent two weeks in bed; since then he has been up and about. Since the onset of illness, five months ago, he had had at least three to six stools a day. He has not, however, restricted his diet and he is eating much the same food as when he was well.

P. E.—T. 98.6°. P. 70. R. 18. B. P. 150/98.

A fairly well developed negro, appears undernourished and looks sick. There is widespread anasarca with soft pitting edema over the legs, abdomen, back, chest and arms. In the edematous areas skin is smooth and shiny. Fingers show some clubbing. There is some pallor of the mucous membranes but no cyanosis or dyspnoea. There is some shotty enlargement of the cervical and inguinal lymph nodes; one axillary lymph node enlarged to about the size of pigeon egg. Left pupil slightly larger than right; both react sluggishly to light and accommodation. There is lenticular opacity over the left eye. In the right fundus there is some streaking of the arteries and slight compression of veins by the arteries in crossing. Teeth and gums are in very poor condition and tonsils are enlarged; pharynx slightly injected and there is edema of the uvula. Thyroid gland is not enlarged. Chest large; lungs are everywhere resonant. Breath sounds in right interscapular region are high pitched. Expiration is prolonged. At both bases there are numerous moist rales. P. M. I. is poorly seen in 5th left I. S., $8\frac{1}{2}$ cm. from midline. There are no shocks or

thrills. Heart is not enlarged to percussion. Dulness: 3.0 $\left\{ \begin{array}{l} (3) 5.5 \\ (4) 7.5 \\ (5) 9.0 \end{array} \right.$

Retromanubrial dulness measures about 4 cm. Sounds are of moderate intensity with a soft systolic murmur localized at the apex. At the aortic area sounds are loud with a slightly harsh systolic murmur. Second aortic sound is louder than pulmonic. Radial pulses are equal. Blood pressure 150/98. Abdomen is somewhat enlarged with slight bulging of flanks where there is dulness. Fluid wave can be obtained. Liver, spleen and kidneys are not felt. External genitalia are normal. Prostate is slightly enlarged. Deep tendon reflexes, including biceps, triceps, periosteal-radials, knee jerks and ankle jerks are hyperactive but equal. There is no ankle clonus; no Babinski. Abdominal reflexes are equal.

Blood examination.—Hbg. 68%; R.B.C. 3,550,000; Leucocytes 8,400; Differential: P.M.N. 64%; P.M.B. 0%; P.M.E. 12%; Juvenile 4%; Lymph. 17%; Mono. 3%. Blood smears show some anisocytosis but no poikilocytosis. There is central achromia. No nucleated R.B.C. No malarial parasites are seen. Wassermann reaction negative. Stools: brown, watery, very little fecal material; show flecks of fresh blood. Benzidine 4+. Mic.—There are numbers of R.B.C. and leucocytes.

Urine.—Clear, amber, 1011, acid, no sugar, albumen faint trace, no sediment, occasional leucocytes, no R.B.C. or casts. Reaction for bile negative. Trace of urobilin.

September 15, after repeated examinations of stools on warm stage, very active amoeba histolytica were found in great numbers. Many of them contained R.B.C. Teleroentgenogram shows infiltration of right lower lobe associated with shadow in the pleura extending upwards along the anterior axillary border. Heart measurement 8.6 cm. to left; 4.7 cm. to right. Width of aorta 0.5 cm.

Blood chemistry.—Nonprotein nitrogen 26; sodium chloride 512 mg.%; CO₂ 57.9 vols.%; cholesterol 120 mg.%; total proteins 3.77 Gm.%; A/G ratio = 38/62.

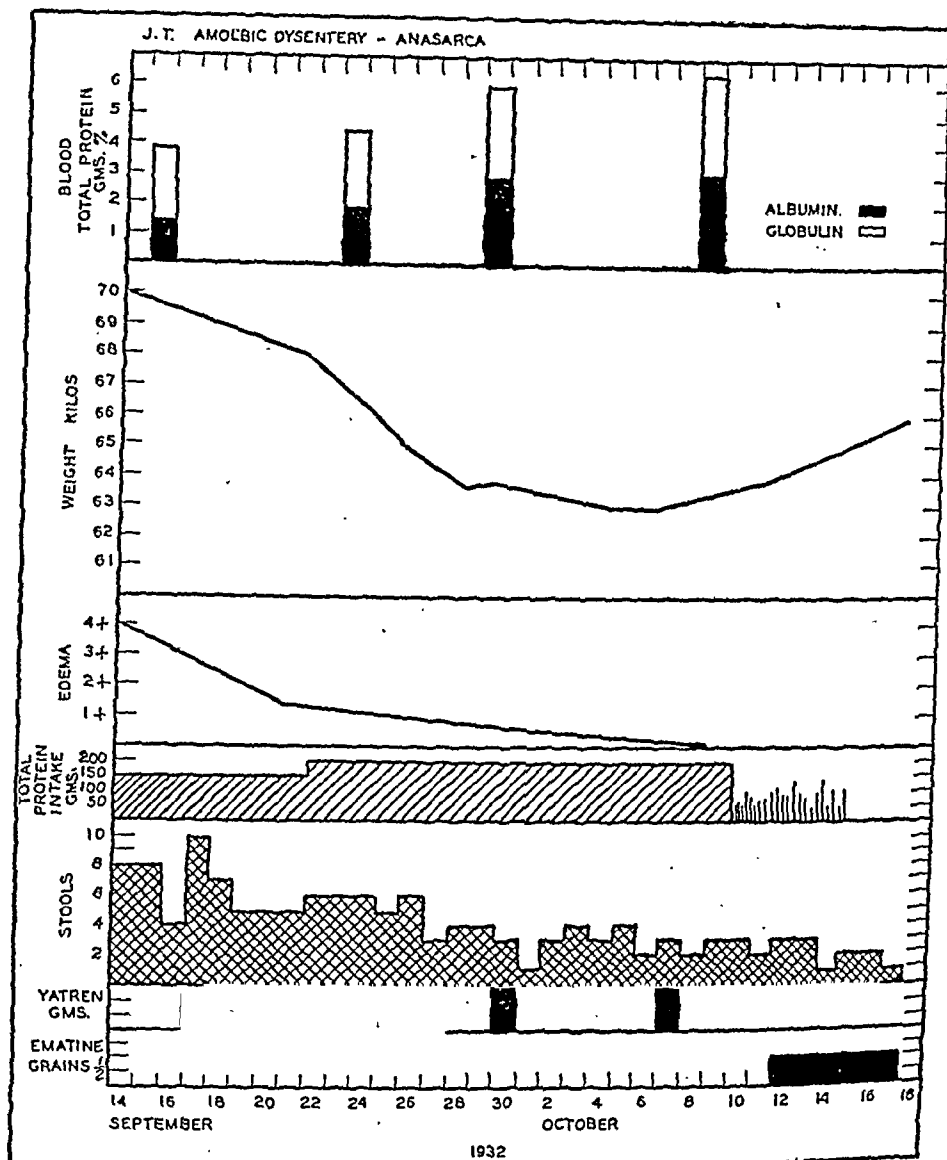
Electrocardiogram shows normal sinus rhythm. P.R. interval is 0.17 sec. T II and T III isoelectric. Levogram. Occasional ventricular extrasystoles.

Summary of positive findings.—Undernutrition; anasarca; amoebic dysentery with hypoproteinaemia; clubbing of fingers; pallor; enlargement of axillary lymph nodes; cataract of left eye; rales at lung bases; systolic murmur at apex and in aortic area; slight elevation of blood pressure; moderate anaemia.

Course in hospital.—Patient was placed on salt poor, low residue diet containing 120 Gm. protein and was allowed 2500 cc. of fluid. On September 18, he was started on yatren in 3 Gm. doses which was continued for ten days, administered alternately by mouth and by enema. At this time rectosigmoidoscopic examination by Dr. Paulson showed that the mucosa was pale, but that there was no frank ulceration. Estimation of protein in the supernatant fluid of stool, made by Esbach method, showed 6 Gm., protein per liter. The blood calcium was 9.4 mg.%; the blood phosphorus 4.1 mg.%. Patient's condition rapidly improved and by September 20 stools had diminished from eight to ten a day to five a day. There was much less blood and mucus in the stools which now contained more fecal matter. Amoeba were no longer seen. The edema started to subside, and on September 21 the protein in the diet was increased to 200 Gm. September 23, phthalein first hour 40%, second hour 15%, with a total of 55%. By September 23 the patient felt very much better; the edema continued to decrease and he had lost eight pounds in weight, from 154 to 146 pounds. The total protein in the serum had increased to 4.34 Gm.% and the A/G ratio was 41/59. The anaemia, however, still persisted—Hbg. 55%; R.B.C. 3,110,000. By September 29 patient felt well; he had lost six more pounds in four days. The nonprotein nitrogen of the blood was 23 mg.%; total proteins had increased to 5.94 Gm.% and the A/G ratio was 45/55. By October 2 the edema had almost disappeared. Stools were soft, brown, well formed, only from two to three a day, and there was no gross blood or pus, though Benzidine was still 4+. B.P. 175/100. By October 7, twenty-four days after admission, the edema had entirely disappeared. Hbg. 80%; R.B.C. 4,700,000. B.P. 128/78, and on the next day the nonprotein nitrogen was 36 and the total proteins of the plasma had increased to 6.39 Gm.%. A/G ratio was 48/52. The weight had diminished to 239½ pounds and he had lost about fifteen pounds in weight since admission. From October 18 to October 22 he received 40 mg. of emetin a day, and his recovery was complete and satisfactory. On October 14 the nonprotein nitrogen of the blood was 35 mg.%; total proteins 5.98 Gm.%; A/G ratio 48/52. October 16 phthalein 50% first hour, 35% second hour, with a total of 85% in two hours. B.P. was 132/88. By October 24 he was up and walking around

and convalescing. Nonprotein nitrogen of the blood was 30 mg.%; total protein 6.29 Gm.% and A/G ratio 51/49. He had gained weight up to 148½ pounds without showing the presence of edema. Stools were normal. The

CHART CASE I.



Showing the variations in the total protein and total albumen globulin of the blood plasma, changes in weight, estimated changes in edema, amount of protein in the food, number of stools per day and treatment. The columns represent the total protein of the blood plasma, the section in black the albumen, the section in white the globulin. It is to be noted that there is a parallelism between the rise in total proteins and total albumen of the plasma, and the loss of weight and decrease in the anasarca.

urine showed specific gravity varying from 1008 to 1016, was continuously acid, no sugar, no albumen, no R.B.C., no casts, occasional leucocytes. He left the

hospital on October 28 having been relieved entirely of the amoebic dysentery and without edema.

The chart shows the course of his illness as well as data obtained from special examinations and the results of therapy.

The prominent features in this case are the presence of anasarca in combination with amoebic dysentery in a patient whose diet was not restricted. There was a striking association between the unusually low plasma proteins and the edema, and between the rapid disappearance of the edema and the synchronous rise in the plasma proteins during the administration of a diet high in protein.

The cause of the deprivation of protein in this patient could not be ascribed to a deficient diet, but was obviously due to a loss of protein in the stools. A single rough calculation showed that the stool contained 6.0 Gm. of protein per liter. Since the stools contained blood, mucus and pus, a part of this protein must have been actually lost from the body, but the remainder came from the protein of the food which had not been absorbed. One may assume, therefore, that the body was deprived of protein in these two ways. There can be little question but that the edema was dependent solely upon the lowered osmotic pressure of the plasma due to its small protein content. A total plasma protein of 3.77 Gm. per cent. is exceedingly low, the average normal ranging from 6.2 to 8.0 Gm. per cent.; and an albumen fraction of 1.37 Gm. per cent. is unusual the average normal ranging from 3.6 to 5.0 Gm. per cent. It seems clear, therefore, that the plasma proteins were reduced far below the level at which edema is usually observed. Though there was no evidence of myocardial failure, the blood pressure was slightly elevated, and it is to be noted that the patient was up and about during most of his illness, a factor which exaggerates most forms of edema. The very rapid improvement and complete symptomatic recovery, with return of plasma proteins to a normal figure, three weeks after admission to the hospital took place during the control of the dysentery and through the administration of a salt poor diet containing 150 to 200 Gm. of protein.

The second case, though somewhat similar in nature, presents differences which are worthy of notice, for though the woman of fifty-six had persistent diarrhea there was, in addition, a serious deficiency in her diet.

CASE 2.—N. I. female; white; age fifty-six; widow; Unit No. 45759, was admitted to the Johns Hopkins Hospital on October 8, 1932, complaining of weakness, anorexia, diarrhoea, nausea and sore tongue.

F. H.—Unimportant.

P. H.—She had measles, diphtheria and tonsillitis as a child; typhoid at nineteen, without complications; bronchitis in 1919 and had suffered from sick headaches most of her life. She had never had breathlessness or swelling of feet and had considered herself healthy. She had taken an enema daily since 1908 for the relief of constipation. Menstruated at fourteen, always regular. Menopause at forty-eight. Married twenty-six years; two children—twenty-one and twenty-four. Miscarriage in 1917 at four and a half months. Best weight 170 lbs. two to three years ago.

P. I.—On June 4 patient slipped on floor, fractured the neck of left femur; was taken to the hospital and placed in traction splint, in which she remained for the next six weeks. The experience was very difficult for her, and the hospital food did not agree with her. She was constipated and her bowels moved only after enemas. She had pains in the stomach. There was no nausea or vomiting. July 16, two months and twenty-three days after admission, patient was put in double cast. Received enemas every day and milk of magnesia once or twice a week. Appetite was very poor. One month and twenty-six days before admission, two weeks before first cast was taken off, diarrhoea began (August 16, 1932). Patient was given chalk, HCl, saline irrigations, and the enemas were discontinued. Her bowels sometimes moved involuntarily six times at night and from ten to twelve times a day. Finally patient stopped eating for three to four days in an attempt to check diarrhoea. There was never nausea or vomiting. Three days ago, September 16, cast was removed, but she was unable to sit up. Diarrhoea continued, though less marked, and she did not eat. About seven days before admission, mouth became sore and tongue swollen; four days before admission she became nauseated; three days before admission patient left hospital. While at home she was so weak that she could not move her legs; was nauseated at the thought of taking food and could not keep water on her stomach. She has had bed sore on sacrum since September 17. Has lost a great deal of weight during her illness.

P. E.—T. 98. P. 116. R. 20. B.P. 110/70: Patient is a small, elderly white woman, very uncomfortable and in much distress. Shows marked pallor with sallow skin and absent teeth. Respirations are regular but slow; alert mentally. Skin is pale and dry with evidence of recent loss of weight, although subcutaneous fat fairly abundant. There are no petechiae or hemorrhages but a superficial area of desquamation over the sacrum. Motion of legs restricted with loss of voluntary motion of left leg and weakness of right. Left hip is apparently healed in good position, with no gross bony abnormalities. Pupils are regular; react actively to light and accommodation; eyes normal. Marked pallor of lips, but tongue is red, raw, with tender ulcerations on tip; large white ulcerated area on left side, and papillary atrophy. Tonsils are small. Thorax is large, percussion note is hyperresonant; breath sounds are distant without rales. Heart: no precordial impulses noticed. Dulness:

4.0 (4) 7.5
(5) 9 P.M.I. is not seen; heart sounds are distant, of fair quality without murmurs. Aortic second is louder than pulmonic second. Pulses are equal,

regular and vessel wall is readily compressible. Abdomen appears obese without distention or tenderness, but shows considerable muscular resistance. No masses are felt. Liver, spleen and kidneys are not felt. Moderate pitting edema of both ankles. Biceps, triceps and periosteal radial reflexes present and active. Knee and ankle jerks are not obtained and there is no Babinski. Vibratory sensation and sense of position are apparently intact.

Urine.—Clear, 1020, acid, sugar—trace, no albumen, sediment +, no R.B.C., no casts, leucocytes 10–15 per high power field, acetone +++, diacetic acid +++. Subsequent urine examinations showed on October 12 and October 13 traces of sugar, + albumen, sp. gr. 1012–1018, no R.B.C., no casts, few leucocytes, no bile or urobilin. By October 13 diacetic acid and acetone had disappeared. From October 31 to December 18 urine was usually neutral or alkaline, low sp. gr. 1010–1020, with + to ++ albumen, great numbers of leucocytes. After October 19, 1932, urine rarely contained albumen, leucocytes were greatly diminished and reaction was acid. Wassermann reaction negative. Nonprotein nitrogen 25 mg. per 100 cc.

Summary of positive findings.—Obesity, edema, sacral bed sores, weakness of legs, complete adentia, glossitis, undernutrition with probable avitaminosis and hypoproteinaemia.

Course in Hospital.—Patient appeared very ill. She was given a transfusion of 500 cc. of citrated blood on October 11, and feeding was started by nasal catheter. During the next few days she was lethargic, the oedema had increased, stools were still numerous, liquid; there was no gross blood or pus; no ova or parasites seen. Benzidine was 4+. Pallor persisted, tongue remained red and dry with erosions at the tip; abdomen was distended, the muscles were tense. By the nasal catheter liquid diet consisting of egg nogs, orange juice, dilute HCl, Brewer's yeast and cod liver oil were administered. She received by continual vena clysis approximately 2400 cc. of salt solution a day. She voided only small amounts of urine, the edema increased, and the plasma proteins fell, as may be seen by the table; the anaemia increased. October 13 and October 14 1 cc. of salyrgan was administered through the vena clysis. Urine increased after the first dose to 1250 cc. in twenty-four hours. Patient seemed somewhat brighter but the edema did not diminish. On October 13 diarrhea continued. Theocin 0.3 Gm. t.i.d. was given for three days. The vena clysis was stopped and by October 16 the patient was able to take 3040 total calories containing Protein 110, Fat 200, Carbohydrate 200, with 2500 cc. fluid through nasal catheter without nausea or vomiting. She began to improve and the edema diminished somewhat. On October 18 a second transfusion of 500 cc. of blood was given. On the same day agglutination for *B. dysenteriae* Shiga was positive in the patient's serum in 1–80 dilution. There was no agglutination for *B. typhosus* or paratyphosus A and B, or with *B. dysenteriae* Flexner. By October 20 agglutination with *B. dysenteriae* Shiga was positive with the serum in 1–160 dilution. During the next few days the patient improved considerably and the edema started to subside. Bismuth subcarbonate and paregoric were used to control the diarrhea. Cultures from the stools did not show either *B. typhosus* or *B. dysenteriae*. B.P. was 90/68. By November 9 patient had improved considerably, though there was still edema of the lower extremities and diarrhea persisted. Nonprotein nitrogen of the blood was 24 mg.%; sodium chloride 396 mg.%;

cholesterol 150 mg.%; and the total proteins in the serum albumen had increased. On the same day cultures from the stools showed on the first and only occasion *B. dysenteriae* Shiga; the same organism was obtained from the urine in culture. From this time on convalescence was slow. She developed ulcers on the left heel, and though *B. dysenteriae* was not again obtained from the stools, it was obtained on November 28, a second time, from the urine. By December 12 B.P. had risen to 104/80 and the stools, though dark brown, gave a negative Benzidine test. Peripheral oedema decreased slowly and the ulcers on the heel improved. By January 17 the nonprotein nitrogen of the blood was 27 mg.% and the total proteins had risen slightly to 4.63 Gm.%. By December 5 the edema had disappeared, tongue was no longer red and sore, patient was up and about, and the total blood proteins, as shown in the table, had risen to 5.25 Gm.%. From this time on convalescence was

BLOOD

Date	Hbg.	R.B.C.	Lets.	P.M.N.	Lymph.	Monos.	Myelocytes
10/8.....	65%	3.63	9,140	88%	10%	1%	1%
10/14.....	68%	3.56	9,200				
10/19.....	66%	3.37					
10/27.....	82%	4.27	9,600				
11/22.....	50%	2.55	9,960				
12/2.....	58%	3.09	7,040				
12/9.....	60%	2.28	7,530				
12/21.....	64%	3.66	6,720				
1/4.....	78%	3.38	8,600				
1/26.....	85%	3.25	8,680				
2/2.....	86%	4.34	7,600				
2/12.....	90%	4.35	8,400				

BLOOD PROTEINS

Date	Total prot. Gm. %	Serum alb. Gm. %	Serum glob. Gm. %
10/10.....	4.60		
10/11.....	4.34	1.95	2.39
11/9.....	4.58	2.34	2.24
1/17.....	4.63		
2/5.....	5.25		
2/7.....	5.38	2.58	2.80
3/23.....	5.31		

uneventful. Blood pressure varied from 123/100 to 140/94. There was no return of the edema and the patient finally left the hospital in April, 1933, having completely recovered. The table shows the changes in the blood count and in the proteins of the blood plasma.

This patient, who, before her accident, had been perfectly well, developed her illness while under treatment for a fractured leg. The illness seems to have been dependent upon partial starvation, due to anorexia, and an infection of the intestinal tract by *Bacillus dysenteriae* Shiga. The combination of malnutrition and dysentery with uncontrollable diarrhea led to an avitaminosis, anaemia, hypoproteinaemia and marked generalized edema. It is noteworthy that, for a short period after admission to the hospital, when fluid was administered by vein, the edema increased and the plasma proteins diminished. Since it was very difficult to control the diarrhea and to administer a high protein diet by mouth, improvement was very slow and it was four months before the edema disappeared entirely, and before the proteins of the blood plasma rose to 5.3 Gm. per cent., approaching the critical level below which edema is likely to occur.

It is probable that the hypoproteinaemia with the consequent edema in this patient was due to three causes; first a greatly diminished intake of protein, which amounted almost to starvation; secondly to decreased absorption of protein from the gastro-intestinal tract associated with the prolonged and excessive diarrhea, and thirdly to the loss of small amounts of protein from bleeding into the intestinal tract and oozing from the inflammation of the mucosa of the colon. The albuminuria was so slight and so transient that it does not seem likely that it could have produced much effect. Recovery ensued when the diarrhea ceased, and when the patient was able to take proper quantities of food.

These two cases illustrate the insidious manner in which extensive edema may arise in patients who are, in one way or another, deprived of amounts of protein that are necessary to maintain the proteins of the plasma at or near their normal level. It is highly important to recognize these forms of edema, for in such instances the use of diuretics, such as were employed at first in the treatment of the second patient, are of little or no avail. It is obvious that the essential procedures consist in correcting, if possible, the abnormality that leads to the loss of protein and in furnishing the starving body

with sufficient protein to meet its excessive needs. A diet containing 120 to 150 Gm. of protein is usually necessary; and, for short periods, as much as 200 Gm. of protein may be given. Transfusions are of some value though the benefit derived from them is usually transitory. Complete rest in bed is essential.

SUMMARY

An account of two patients is recorded who suffered from excessive edema, associated with abnormally low plasma proteins. The origin of the hypoproteinaemia, which appeared to be the essential, or, indeed, sole cause of the edema, was due to protein starvation arising from protein deprivation. This was brought about in the first patient, who was on an adequate diet, by amoebic dysentery; and in the second patient by a combination of bacillary dysentery and completely inadequate diet. The first patient recovered with remarkable rapidity when the dysentery was properly treated and when he was fed a diet high in protein. The second patient improved slowly, in all probability because of the difficulty of feeding and because of the intractability of the diarrhea.

REFERENCES

- ¹ VAN SLYKE, D. D., AND PETERS, J. P.: "Quantitative Clinical Chemistry," Vol. 2, Williams & Wilkins Company, Baltimore, 1932.
- ² ELWYN, H.: "Edema and Its Treatment," The Macmillan Company, New York, 1929.
- ³ VOLHARD, F.: "Die doppelseitigen hämatogenen Nierenerkrankungen," *Hand. der Inn. Med.*, 6:1, 1931.
- ⁴ GOVAËRTS, P.: "Role des Propriétés Physico-Chimiques der Protéines dans la Pathogénie des Oedemas," *Extrait des rapports du XIX Congrès Français de Médecine*, Paris, 1927; "Considérations sur la Pathogénie des Oedèmes et les échanges Hydriques de l'Organisme," *Extrait des Ann. et Bull. de la Soc. Royale des Sci. Méd. et Naturelles de Bruxelles*, No. 5-6, 1932.
- ⁵ PETERS, J. P.: "Salt and Water Metabolism in Nephritis," *Medicine*, 11:435, 1932.
- ⁶ LEITER, L.: "Nephrosis," *Medicine*, 10:135, 1931.
- ⁷ LANDIS, E. M., AND LEOPOLD, S. S.: "Inanition Edema Associated with Tuberculous Enteritis; Mechanism of Production of Edema," *J.A.M.A.*, 94:1378, 1930; "Micro-Injection Studies of Capillary Permeability," *Am. J. Physiol.*, 82:217, 1927; "Micro-Injection Studies of Capillary Pressure in Mammalian Mesentery," *Am. J. Physiol.*, 85:387, 1928.
- KROGH, E. A., LANDIS, E. M., AND TURNER, A. H.: "The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to

- the Colloid Osmotic Pressure of the Blood," *J.Clin.Investigation*, 11:63, 1932.
- * EPSTEIN, A. A.: "Concerning the Causation of Edema in Chronic Parenchymatous Nephritis; Methods for Its Alleviation," *Am.J.M.Sc.*, 154:638, 1917.
- * LEITER, L.: "Experimental Edema," *Proc.Soc.Exp.Biol.& Med.*, 26:173, 1928; "Experimental Nutritional Edema," *Arch.Int.Med.*, 48:1, 1931.
- ¹⁰ BARKER, M. H., AND KIRK, E. J.: "Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients," *Arch.Int.Med.*, 45:319, 1930.
- ¹¹ MEYERS, W. K., AND TAYLOR, F. H. L.: "Hypoproteinaemia Probably Due to Deficit Formation of Plasma Proteins," *J.A.M.A.*, 101:108, 1933.
- ¹² PETERS, J. P., BULGER, H. A., AND EISENMAN, A. J.: "The Plasma Proteins in Relation to Blood Hydration; I. In Diabetes Mellitus," *J.Clin.Investigation*, 1:451, 1925; III. The Plasma Proteins in Malnutrition, *Ibid.*, 3:491, 1927.
- ¹³ YOUNG, J. B., BELL, A., DONLEY, D., AND FRANK, H.: "Endemic Nutritional Edema, I. Clinical Findings and Dietary Studies," *Arch.Int.Med.*, 50:843, 1932; "Endemic Edema," *J.A.M.A.*, 99:883, 1932.
- ¹⁴ WEECH, A. A., AND LING, S. M.: "Nutritional Edema. Observations on Relation of Serum Proteins to Occurrence of Edema and to Effect of Certain Inorganic Salts," *J.Clin.Investigation*, 10:869, 1931.

THE PATHOGENESIS OF ANTERIOR POLIOMYELITIS, A REVIEW*

By THELMA LOVETT, M.A.

Philadelphia, Pennsylvania

PATHOGENESIS OF ANTERIOR POLIOMYELITIS

ROUTES OF INVASION OF THE CENTRAL NERVOUS SYSTEM

I. Invasion by way of the nerve fibers.

Anatomical basis.

Evidence in favor of invasion by way of the nerve fibers.

- A. Injury to the nerve cells is the primary lesion in the nervous system.
- B. Sequence of infection follows known fiber pathways.
- C. Methods of inoculation which bring the virus into intimate contact with axis-cylinders are the most effective in establishing the disease.
- D. Predominance of paralysis in the lower limbs has occurred regardless of the route of inoculation used.
- E. Meningeal involvement is secondary to infection of the nervous tissues.
- F. Transection of the spinal cord and experimental poliomyelitis.

II. Invasion by way of the blood stream.

Anatomical basis.

Possibility of embolism and thrombosis in poliomyelitis.

Evidence in favor of invasion by way of the blood stream.

- A. Animal experiments.
- B. Pathology of the disease.
- C. An explanation of the absence of the virus in the blood.
- D. Part played by the peripheral ganglia in infection.

Evidence in favor of invasion by way of the blood stream

* From the Department of Pathology and the Laboratory of Orthopaedic Research, School of Medicine, University of Pennsylvania, Philadelphia. Compiled under the direction of Doctor George Wagoner.

combined with passage of the virus through the cerebrospinal fluid.

- A. Experimental poliomyelitis produced by intravenous inoculation.

III. Invasion by way of the lymphatics.

Anatomical basis.

Evidence in favor of invasion by way of the lymphatics combined with passage of the virus through the cerebrospinal fluid.

- A. General lymphatic hyperplasia.
- B. Methods of inoculation with relation to the perineural lymphatics.
- C. Analogy to cerebrospinal meningitis.
- D. Primary meningeal involvement.
- E. Passage of the virus through the cerebrospinal fluid.
 - 1. Occurrence of the virus in the spinal fluid.
 - 2. Intrathecal inoculation.
 - 3. Aseptic meningitis.
 - 4. The value of immune serum given intraspinally.
- F. Changes in the perivascular spaces and interstitial inflammation constitute the primary lesions in the central nervous system.

Summary.

PORTALS OF ENTRY

- I. Nasopharynx.
- II. Gastrointestinal tract.

Summary.

INTRODUCTION

If the virus of poliomyelitis enters the body through the nasopharynx or the gastrointestinal tract, it may, conceivably, invade the central nervous system by way of the blood stream, the lymphatics, or the fibers of the peripheral nerves. The purpose of this paper is, first, to review our knowledge concerning each of these three possible routes of invasion, and second, to review the evidence

pertaining to the nasopharynx and the gastrointestinal tract as possible portals of entry. In any discussion of experimental poliomyelitis it is essential to remember that the lower animals, including monkeys, are not naturally susceptible to the disease. The details of the infection in lower animals may differ greatly from those in man where spontaneous infection occurs.

ROUTES OF INVASION OF THE CENTRAL NERVOUS SYSTEM

I. Invasion by Way of the Nerve Fibers

Anatomical basis.

The central nervous system, consisting of the brain and spinal cord, is in direct communication with all parts of the body through twenty-four (twelve pairs) of cranial nerves, and sixty-two (thirty-one pairs) of spinal nerves. The structural unit of the nervous system is the neurone, (or the nerve cell body with its processes).

The *gray matter* of the nervous system is composed chiefly of the cell bodies of the neurones and naked axis cylinders. It is confined, primarily, to the following locations: the cerebral and cerebellar cortices; the olfactory bulb; the basal ganglia and nuclei of the brain; the brain stem; the anterior and posterior gray columns of the spinal cord; the dorsal root ganglia of the spinal nerves; the sensory ganglia of the fifth, seventh, eighth, ninth, and tenth cranial nerves; and the ganglia of the autonomic nervous system, including the ciliary, otic, sphenopalatine, submaxillary, the ganglia of the sympathetic trunks, the collateral ganglia along the aorta—especially the celiac, mesenteric and aorticorenal—and lastly the terminal autonomic ganglia located close to or within the structures they innervate.

The *white matter* of the nervous system is made up of the processes of nerve cells or the nerve fibers—both myelinated and unmyelinated. The axis-cylinder of the nerve fiber is composed of delicate neurofibrils embedded in a semifluid neuroplasm. In myelinated fibers the axis-cylinder is surrounded by a thick sheath composed of a fatty substance, myelin, supported by a reticulum of neurokeratin. A nucleated, membranous, neurilemmal sheath is found on all fibers of the peripheral nerves, but is not present on fibers within the brain and spinal cord. White matter is found in the commissures and association bundles of the brain; the pro-

jection pathways connecting the cerebral cortex with the brain stem, the fiber tracts of the spinal cord, and the peripheral nerves.

A peculiar supporting tissue of ectodermal origin, called neuroglia, occupies the interstices among the true nervous elements of both the white and gray matter.

Evidence in Favor of Invasion by Way of the Nerve Fibers.

Fairbrother and Hurst,³² and Hurst^{65, 66} have presented evidence to show that after intracerebral, intranasal, intraneural and intrathecal inoculation into monkeys, the virus of poliomyelitis spreads mainly by the axis-cylinders and that the cerebrospinal fluid plays a minor part in disseminating the infection. In support of this contention, several points may be emphasized:

A. *Injury to the nerve cells is the primary lesion in the central nervous system.*—Primary meningeal, perivascular and interstitial lesions have long been described as evidence of the transmission of the virus through the blood stream and lymphatic channels. Hurst⁶⁴ has attributed this conception of the disease to the examination of postmortem human or experimental material in which the primary lesions were obscured by advanced pathological changes. Investigating early cases of the experimental disease in monkeys, he has found primary degeneration of the nerve cells, which he has cited as evidence of axonic transmission of the virus. Necrosis of nerve cells, according to this author, occurred where very few vessels were affected synchronizing with, rather than following the vascular changes. Primary injury to the nerve cells had previously been described^{100, 12, 9, 13}) and Greenfield⁵⁸ has since reported similar observations. Landsteiner, Levaditi, and Pastia⁸² have reported severe neurone damage in the absence of marked perivascular inflammation; while Schreiber¹¹⁹ has concluded that injury to the nerve cells results from a direct toxic action, supplemented by edema. Burrows¹⁰ has contradicted the work of Hurst. From the examination of post-mortem human material, he has found perivascular and interstitial lesions primary, and would attribute Hurst's observations to the violent reaction which occurs in experimental animals infected by massive doses of the virus. (The work of Burrows is discussed more fully under the question of lymphatic transmission of the virus—see Section III.)

B. *Sequence of infection follows known fiber pathways.*—The

spread of the virus within the central nervous system has been traced by two methods—intracerebral inoculation of monkeys to detect the presence of the virus in the tissues of the inoculum; and microscopical study of the tissues for histopathological evidence of the disease, the latter having proved more satisfactory in the study of cortical lesions where, presumably, the virus is attenuated.³² Fairbrother and Hurst³² have found that following parietooccipital inoculation, lesions appeared first in the homolateral thalamus, hypothalamic nuclei, around the third ventricle and then in the mid-brain, and pons. Following intranasal inoculation there were lesions first in the olfactory bulbs, and later in the basal cortex and mid-brain. After infection of the midbrain and pons, the lesions appeared simultaneously at many levels of the medulla and cord, and spread upward into the contralateral thalamus and cortex, gaining no foothold in the cerebral cortex except where the great projection pathways ended around the central sulcus. Foci were observed near the basal cortex only after intranasal inoculation, with relatively less involvement of the basal ganglia in those cases than was seen after intracerebral inoculation. After intracerebral inoculation the contralateral leg was most often involved first,¹¹⁶ while after intrathecal inoculation with involvement of the lumbar motor apparatus the cortical lesions appeared first about the precentral gyrus and predominated there.⁶⁶ Homolateral predominance of lesions was noted after intranasal³² and intraneural⁴⁹ inoculations. A case of polioencephalo-myelitis in a boy has been described by Goodpasture.⁵⁶ The medullary lesions appeared to be directly related to the central distribution of the ninth and tenth cranial nerves. All of these findings are suggestive of transmission of the virus along known fiber pathways. Inflammation in the white matter is rare. Until the fibers lose their myelin sheaths, according to the axonic theory of transmission, the virus seems to be insulated. Poliomyelitis is then a disease travelling by nerve fibers and manifesting itself only in areas containing nerve cells,³² supposedly seeking the nerve parenchyma to multiply.^{36, 45}

C. *The methods of inoculation which bring the virus into intimate contact with the axis-cylinders are the most effective in establishing the disease.*—The intracerebral route (first used by Flexner and Lewis⁴⁷), by putting the virus in direct contact with the axis-cylinders, has been the most effective.^{50, 33, 43, 62, 123, 86, 87, 78, 48} The

intranasal route, though irregularly effective,^{32, 80, 41, 80, 53} was classed second to the intracerebral³⁴ and has been considered by many to be the natural route of infection in man.^{34, 56} Effectiveness of the intraneural route^{134, 96, 45, 40, 107} has depended upon the degree of trauma to the axones.³² Some experimenters have regularly produced infections by intrathecal inoculation, using very virulent agents.^{15, 126, 51, 106, 116} Intraocular inoculation^{36, 79} may be one of the most satisfactory methods while the subcutaneous,¹⁰⁶ intravenous^{74, 36, 16, 35, 39} and intraperitoneal^{88, 85, 104, 83} have been difficult, and only rarely has infection been successfully established by their use.

D. *Predominance of paralysis in the lower limbs has occurred regardless of the route of inoculation used* and therefore cannot be considered as indicative of invasion by the gastrointestinal lymphatics. Romer¹¹⁶ has described the Landry syndrome with paralysis starting in the legs in a case of experimental poliomyelitis produced by intracerebral inoculation. The onset and predominance of paralysis in the lower limbs^{131, 94, 50} is essentially the same for all routes of inoculation indicating that it is due to some special susceptibility of the lumbar anterior horn cells, or especially favorable conditions for growth of the virus in that locality.³² Predominance of paralysis in the lower limbs cannot, therefore, be indicative of entrance of the virus through the gastrointestinal lymphatics as was cited by Wickman.¹³²

E. *Meningeal involvement is secondary to infection of the nervous tissues.*—1. *The sequence of lesions* within the central nervous system and the meninges has been cited in support of this view. Walter¹²⁶ has reported inflammation of the spinal cord falling off from within outward, while Landsteiner, Levaditi, and Pastia⁶² have described areas of inflammation within the cord independent of any overlying meningitis. Schroder¹²⁰ considered pial infiltration to be due to cells that had passed out of the cord from the perivascular spaces. Hurst⁶⁴ has found infiltration of the spinal meninges only when an infiltrated vessel from the deeper tissues reached the surface of the spinal cord. Again, Fairbrother and Hurst,³² investigating the early stages of the disease in monkeys, have reported the following sequence of lesions:

First to second day—Meningitis spread over the hemispheres, with lesions in the nervous tissues only at the site of inoculation.

Second to Third day—No direct spread of meningitis to the brain stem, pia involved only where an infiltrated vessel from the deeper tissues reached the surface.

Fifth day—When paralysis set in, the meningeal reaction was found to be variable but cellular foci in the deeper layers of the cortex were always independent of an overlying meningitis. Pial infiltration was insignificant until a late stage of the disease and not present at all levels where there were changes in the gray matter. Meningitis was not sufficient to account for the early symptoms. The same authors have also reported infection by the intranasal route without involvement of the meninges. They conclude that unless the virus can spread through the meninges without causing inflammation, the absence of involvement of the meninges of the brain stem and cord in early cases, indicates that the infecting agent has traveled by other paths.

2. *The virus has never been found in the cerebrospinal fluid or blood of human cases.*² Only on rare occasions has it been found in the spinal fluid in cases of the experimental disease in monkeys and in these instances only under peculiar circumstances. The presence of the virus in the spinal fluid has been reported following massive cerebral injections;^{47, 49, 1} when all the dose was believed to have been injected into the ventricle;^{51, 32} after massive blood injections or following aseptic meningitis;^{38, 37, 42, 35, 39} after intraspinal injection of massive doses;^{126, 60} and after intrasciatic inoculation in three cases.⁶⁵ Against these occasional positive findings, there has been a whole series of negative results in man and monkeys.

F. *Transection of the spinal cord and experimental poliomyelitis.*—Jungeblut and Spring⁶⁷ have studied the propagation of the virus in a monkey inoculated by the intracerebral route after complete transection of the cord had been done. The cervical cord (or proximal segment) was found to contain the virus, while the lumbar cord (distal segment) remained normal histologically, in spite of the predilection of the virus for that region, and on inoculation gave no symptoms in a second monkey. Although this work has no direct bearing upon the invasion of the virus from the periphery to the central nervous system, it is of particular interest because, to date, it is the only experimental evidence either in confirmation or con-

tradition of the theory of axonic transmission as enunciated by Fairbrother and Hurst.^{32*}

Faber³¹ has announced that confirmation of axonic transmission will be found in the reports of experiments soon to be published by that author. He has called attention to the point that the early symptoms of poliomyelitis are not necessarily of extraneural origin, and that lymphoid hyperplasia is a secondary phenomenon.

II. Invasion by the Blood Stream

Anatomical basis.

Blood Supply of the Brain.—The cerebral arteries are derived from the internal carotids and the vertebrals which at the base of the brain form an anastomosis known as the “arterial circle of Willis.” Three paired trunks which supply the cerebral hemispheres arise from this circle and are named from their distribution the anterior, middle and posterior cerebral arteries. Each of these principal arteries gives origin to two different systems of secondary vessels. One of these is named the *ganglionic system*, and the vessels belonging to it supply the thalami, and corpora striata; the other is the *cortical system*, and its vessels ramify in the pia mater and supply the cortex and subjacent brain substance. The long or medullary arteries pass through the gray substance and penetrate the subjacent white substance to the depth of three or four centimeters without intercommunicating otherwise than by very fine capillaries. The short vessels are confined to the cortex, where they form, with the long vessels, a compact net-work in the middle zone of the gray substance, the outer and inner zones being meagerly supplied with blood.

The question of “end arteries” in the brain.—Cohnheim²¹ first clearly stated the theory that infarcts could occur only where there was no anastomosis and from his observations the idea of end arteries in the brain has persisted. Lorenti di No,⁹³ Pfeifer,¹¹² Cobb and Talbott,²⁰ and Morgan¹⁰² have presented evidence to show that there are no real end arteries in the brain, but that a particularly rich capillary anastomosis occurs throughout that organ. They attribute infarction to the lack of a normal oxygen supply rather than to anemia.

* The theory of invasion by way of the nerve fibers is supported in recent articles by Rivers¹²⁵ and Marinesco and Dragenesco.¹²⁶

The blood supply of the spinal cord is derived chiefly from one anterior and two posterior spinal arteries, which, arising from the vertebral, descend on the spinal cord and are reinforced by a succession of small branches entering the vertebral canal through the intervertebral foramina. The anterior artery runs the length of the spinal cord in the anterior spinal groove and sends branches, the arteriae centrales about two hundred in number, at regular intervals into the anterior fissure. At the bottom of the fissure each central artery divides into two branches which plunge right and left through the white matter, each to supply an area in the length of the anterior gray column of 1.5 to 2 cm. Although they supply chiefly the anterior gray columns there are branches to the bordering white matter and one posterior branch. Unlike the brain, all the blood supply to the spinal cord appears to come by way of surface arteries and their perforating branches; no vessels are found within the central canal, and no large vessels run for any great distance up and down the cord. Although anastomosis takes place between capillaries from different arterial trees, there is a much less complete anastomosis between segments of the cord than between different parts of the brain. The external white matter is supplied by a number of short perforating branches most of which arise from the two posterior spinal arteries.¹¹¹ The capillaries empty into venules and drain outward to surface veins, both in the cord and in the cerebral cortex.

The arachnoid is a delicate membrane enveloping the brain and medulla spinalis, lying between the pia mater internally and the dura mater externally. The subarachnoid cavity is the interval between the arachnoid and the pia mater. It is occupied by a spongy tissue consisting of trabeculae of delicate connective tissue and intercommunicating channels in which the subarachnoid fluid is contained. This cavity is small on the surface of the hemispheres, but at certain parts of the base of the brain the arachnoid is separated from the pia mater by wide intervals, which communicate freely with each other and are named subarachnoid cisternae.

It is now generally agreed that the *cerebrospinal fluid* is produced largely by the choroid plexus, although some authors believe that the blood vessels of the subarachnoid space and brain take more or less part in its production.^{111, 63} From the lateral ventricles the spinal fluid flows by way of the foramina of Munro into the third

ventricle, and thence by the aqueduct of Sylvius to reach the fourth ventricle, from which it escapes by way of the foramina of Majendie and Luschka into the subarachnoid space. The absorption of the cerebrospinal fluid may be a dual process involving the perineural lymphatics, but it is generally believed to be chiefly a rapid drainage through the arachnoid villi into the great dural sinuses.

The barrier between the blood and the spinal fluid.—Clinical observations and animal experiments have shown that various substances introduced into the blood do not appear in the spinal fluid. Thus there has arisen the theory that a barrier exists between the two, and the nature and location of the barrier has been the subject of many discussions. The whole question is obviously the question of the source and nature of the cerebrospinal fluid. Monakow⁹⁹ has in recent years made a study of the choroid plexus and all tissues that may act as a barrier between the blood and the spinal fluid. The different organs which he includes in the barrier are: choroid plexus, tela choroidea, ependyma, subependymal tissue, neuroglia, and perhaps the vascular endothelium. This function of the choroid plexus is generally accepted. That the tela choroidea also acts in this way is questionable, the indications being that the foramina of Majendie and Luschka are real openings so that the tela is only a partial dam and not a barrier.¹¹³ The ependyma and subependymal tissues separate the ventricular cavity from the brain tissue, but that they normally act as a filter for spinal fluid, allowing it to pass into the brain, is open to grave doubts.¹¹¹

The Possibility of Embolism and Thrombosis in Poliomyelitis

Embolism and thrombosis of vessels of the central nervous system in acute anterior poliomyelitis, suggested by Pierre Marie and supported by Hoche, has long been discountenanced. While Mott,¹⁰³ Money,¹⁰¹ and Batten⁷ report thrombi, such instances are extremely rare and are found only in very late cases. Wickman¹³² dismissed the question by calling attention to the fact that the characteristic, necrotic, embolic areas have not been observed in poliomyelitis, and that the white matter is not involved as would be expected from observation of diseases where emboli do occur.

Evidence in Favor of Invasion by Way of the Blood Stream

A. *Animal experiments.*—Contrary to other experimenters, Krause and Meinicke⁷⁴ have found the virus in the blood and spleen

of children dead of poliomyelitis, and have reported that the blood is the most effective site for inoculation of rabbits, the virus persisting there in the initial stages of the disease.

B. *Pathology of the disease.*—Harbitz and Scheel⁵⁹ have maintained that the virus reaches the pia by way of the blood and then invades the spinal cord along the vessels. Peabody, Draper and Dochez¹¹⁰ have described a picture of the pathology of poliomyelitis in which the distribution of the lesions is correlated with the richness of the blood supply and asymmetry of paralysis is attributed to the irregularity with which the vessels supplying the cord are given off at different levels. The first change noted by these authors was acute interstitial meningitis, most marked on the anterior surface and around the anterior fissure where the vessels enter the cord from the meninges. With the advance of the disease the perivascular infiltration extended along the vessels entering the cord, evidenced by hyperemia, thick collars of small round cells about the vessels, and extensive edema. A toxic effect on the vessel walls was believed to have given rise to the numerous small hemorrhages. The injury to nerve cells was attributed to mechanical pressure of cellular exudate, edema and hemorrhage with the acknowledged possibility of a direct toxic action. Flexner,³³ without definitely accusing the blood of transmitting the disease, has found, from pathological investigations, that vascular lesions constituted the primary causes of lesions in the nervous tissue, and correlated the latter with the richness of the blood supply and the peculiar branching of the central artery in the area.⁵⁰ Injury to nerve cells, he has attributed to anemia, compression, focal hemorrhage and edema. He believed the continued action of these forces resulted in necrosis after which recovery of function was impossible. Saddington¹¹⁷ has reported the presence of sharply defined intravascular lesions in the anterior and posterior spinal veins and lymphatics at the lumbar level following experimental infection in a monkey by the gastrointestinal route. Wickman¹²⁹ has found more lesions in veins than in arteries. Other workers have reported that inflammation was found following the vessels of the meninges to the deeper tissues, and invading also by way of the vessels of the ependymal cavities.⁸⁷

C. *An explanation of the absence of the virus in the blood.*—The virus has never been found in human blood,⁴⁸ nor in the blood of animals later than ten days after intravenous inoculation.² The

presence of the virus in the blood in the preparalytic stage of the disease has been reported in one case where it was found on the seventh day following intracerebral inoculation.¹⁰ Draper²⁶ has suggested that the almost universal failure to detect the virus in the blood during the disease may depend upon, (a) the fact that no instance of human disease has been studied sufficiently early in its course, (b) dilution of the virus in the blood, and (c) low infective power of the virus taken directly from the human.

D. Part played by the peripheral ganglia in infection.—Of the nervous tissues, only the dorsal root ganglia³⁰ and possibly the sympathetic ganglia are capable of removing the virus from the blood.^{45, 104} The virus has been found regularly in the dorsal root ganglia,^{50, 36, 27} also in the Gasserian and sympathetic ganglia.⁴⁴ The presence of the virus in the dorsal root ganglia in the preparalytic stage² takes on an added significance in view of the contention that the multiplication of the virus takes place in the gray matter of the nervous system.^{77, 45}

Evidence in Favor of Invasion by Way of the Blood Stream Combined with Passage of the Virus through the Cerebrospinal Fluid

A. Experimental poliomyelitis produced by intravenous inoculation.—The experiments of Flexner and his coworkers have established the transmission of experimental poliomyelitis by intravenous inoculation.^{36, 37, 38, 16} A mechanism for the rapid removal of the virus from the blood has been indicated.^{35, 39} The virus did not remain long in the blood stream.¹⁶ After enormous intravenous doses it has been found to disappear from the blood within seventy-two hours. Though large intravenous doses of the virus served to transmit the disease, smaller doses failed to do so. The virus was found deposited promptly in the spleen, where it survived for seventeen days, to produce a mild infection in another monkey by intracerebral inoculation. It seemed to be attracted to nervous tissues in general,³⁶ but through the blood was not found able to attack them directly. Following intravenous inoculation the choroid plexus was injured by aseptic meningitis produced by the intraspinal injection of horse serum, whereupon invasion of the central nervous system followed rapidly.^{35, 39} The perivascular lesions were more pronounced in cases of the disease resulting from intravenous inoculation; capil-

laries were seriously damaged, and definite changes noted in the minute vessels of the choroid. Damage to the ependymal cells was seen with marked disturbance of the underlying vessels. Immune serum, given intraspinally, was found effective in neutralizing the virus and preventing the nervous lesions after aseptic meningitis had opened the way for invasion of the central nervous system. Though the disease with paralysis was established by intravenous injection, the lesions were less typical of the human disease than those which resulted from inoculation by the intraneural route.³⁰ Kramer,⁷³ in a recent review, considers this work convincing evidence of the importance of the blood in transmitting the disease.

III. INVASION BY WAY OF THE LYMPHATICS

Anatomical basis.

The relation of the subarachnoid and perineural spaces.—Lymphatic transmission of the virus from the exterior to the central nervous system, must depend upon the existence of some connection between the subarachnoid space and the perineural lymphatic spaces. The perineural space is a potential space between the epineurium and the surface of the nerve bundle, with walls of connective tissue elements.²⁹ Domenico and Cotugno,²² by injections of mercury and air, first demonstrated a distensible space about the larger nerves. The prolongations of the spinal arachnoid along the cranial and spinal nerves have generally been described as blind cul-de-sacs, over which the dura is continued for a short distance peripherally to blend with the epineurium. Histological observations on this point are difficult to interpret and injection experiments have been centered on the passage of substances outward from the subarachnoid space rather than inward in the direction in which the virus of poliomyelitis must travel if it gains entrance to the nervous system by this route. Substances injected into the subarachnoid space have been found to penetrate for varying distances along the spinal and cranial nerves,^{114, 68, 123, 127} giving rise to entirely contradictory conclusions as to the amount of cerebrospinal fluid that may escape by the perineural pathways.^{30, 61} One of the most recent reports on the subject by Dyke and Deery²⁹ gives evidence of the escape of lipiodol along the tenth space for a distance of five centimeters lateral to the margins of the canal, and in the lumbar region, for a distance of ten centimeters out in the general direction of the lumbar plexus.

The perivascular space.—Since Virchow first described the perivascular spaces in the brain there has been much controversy as to their exact anatomical relationships. Recent books differ in their interpretation of histological and physiological observation.^{99, 118, 23} There is practical agreement, however, as to the histological structure of the perivascular space. About the larger vessels it is a distinct entity lying between the elastica externa and the membrana limitans gliae. On both sides it is lined with flattened connective tissue cells which may have a quadrilateral or hexagonal shape and are then called endothelial. There is no doubt as to the presence of this space as an anatomical structure around all the large and small arteries and veins within the nerve tissue, but a well-defined space is not discernible about the smallest arterioles, venules, and capillaries. Microscopically it can be seen that capillaries run close to nerve cells and that there is a perineuronal space which often appears to join the pericapillary space. The fluid in these pericellular and pericapillary spaces can apparently make its way to the more distinct perivascular spaces of the veins and arteries, and here be contained between well-organized endothelial walls. The transition, however, from the ill-defined intercellular fluid spaces, the pericapillary and perineuronal spaces to the clear-cut perivascular spaces, is a gradual one.¹¹¹

The most debated phase of this question at present is whether or not the true perivascular space of Virchow and Robin connects with the subarachnoid space on the one hand and the perineuronal space on the other, to form a drainage system for the brain. In all places it is possible to look on the space as a loosened and irrigated adventitia with more and more organized boundaries as the vessels become larger. Where the surface of the brain is reached, and where the vessel at last empties into the subarachnoid space, a heavy pial layer of connective tissue has to be pierced. This makes a strong ring round the mouth of the vessel which resists dilatation and keeps the mouth of the perivascular space small even though the space behind may be dilated. The flow is in all probability downward from the perineuronal space, as demonstrated by Kubie,⁷⁶ to the perivascular spaces and thence into the subarachnoid space, along both the veins and arteries. Exudates in the subarachnoid space are not likely to enter the perivascular spaces. Schaltenbrand and Bailey¹¹⁸ argue

that there is no normal connection between these various spaces, but the physiological experiments of Kubie⁷⁰ and Weed¹²⁸ indicate that there is a free passage.¹¹¹

Evidence in Favor of Invasion by Way of the Lymphatics Combined with Passage of the Virus through the Cerebrospinal Fluid

A. *General lymphatic hyperplasia.*—Burrows,¹⁰ has made an extensive study of postmortem and clinical cases of poliomyelitis in the 1916 epidemic in Baltimore, and has described a pathological picture of general lymphoid hyperplasia with the constant appearance of inflammation in Peyer's patches. He believes that poliomyelitis should be classed with the diseases of the lymphatic system. Gross enlargement of the lymph nodes was not often marked but it was always present to some degree and, according to this author, was one of the necessary diagnostic signs in the mild and abortive cases. From the rare incidence of symptoms in the nose and throat and the constant involvement of Peyer's patches, he was led to believe that the portal of entry was by the lymphatics of the gastrointestinal tract, from which the virus spread in less resistant cases to the subarachnoid space and perivascular spaces of the spinal cord, medulla and adjacent parts. The exact anatomical course for this route of invasion has not been outlined. General lymphoid hyperplasia has been described by other investigators,¹³³ and the virus has been found regularly in the mesenteric lymph nodes,^{34, 51} even in the experimental disease produced by cerebral inoculation.³³

B. *Methods of inoculation with relation to the perineural lymphatics.*—With the exception of direct intracerebral inoculation, the intranasal and intraneural methods are among the most effective means of producing the experimental disease. The perineural lymphatics of the olfactory nerves constitute the most direct connection between the intrameningeal spaces and the exterior of the body. Methods of inoculation which are unrelated to nerves, and hence to their lymphatics, are among the most difficult means of producing experimental cases of poliomyelitic infection in monkeys (Section I, part C).

C. *Analogy to cerebrospinal meningitis.*—Cerebrospinal meningitis enters by way of the lymphatics of the olfactory nerve, passing through the cribriform plate to the meninges. This has been regarded by Flexner³⁴ and others as the natural route in poliomyelitis.

D. *Primary meningeal involvement*.—Primary involvement of the meninges has been described by Harbitz and Scheel.⁵⁰ The pia was always involved, frequently independently of lesions in the nervous substance though the reverse was never true. Wickman¹³¹ and Strauss¹²⁴ have reported similar findings. Amoss² has reported that meningeal inflammation was the first lesion in the central nervous system. Clark and Amoss¹⁵ recorded meningeal infection without paralysis. Hurst⁶⁴ found meningeal involvement the rule, but associated only with superficial inflammation and not with deep cortical lesions.

E. *Passage of the virus through the cerebrospinal fluid*.—1. *Occurrence of the virus in the spinal fluid*. It has already been pointed out that the virus has been found in the spinal fluid of experimental cases only on rare occasions (I, E, 2.), but even this may be of considerable significance in view of the fact that the virus is rapidly removed from the fluid.^{10, 15, 66} The passage of the virus from the blood through the spinal fluid after massive intravenous inoculation has been demonstrated.^{35, 36, 37, 38, 39} The virus has been found in the spinal fluid in three cases following intrasciatic inoculation.⁶⁵ That the fluid is infective during the incubation period in monkeys following intracerebral inoculation, but not later, has been reported.^{134, 43, 50}

2. *Intrathecal inoculation*. Given a virus of adequate virulence, Clark¹⁵ found that the disease was regularly produced by intrathecal inoculation. This investigator reported that the virus was present in the spinal fluid on the second but not on the sixth day following inoculation, while Hurst⁶⁶ found it present as late as the fifth day. Kubie⁷⁵ showed that a dye can penetrate deeply into the nervous tissues by way of the perivascular spaces, indicating the possible route of invasion of the nervous tissues by virus present in the spinal fluid.

3. *Aseptic meningitis*. Flexner and others^{36, 3} found that aseptic meningitis produced by the intraspinal injection of horse serum aids in establishing the disease by both intranasal and intravenous inoculation. These authors concluded that there was a defense mechanism in the "meningio-choroid complex" and that the spinal fluid was regularly involved in invasion of the central nervous system. Hurst⁶⁵ was successful in producing the disease in only three of

twelve attempts, using several methods of intranasal inoculation combined with aseptic meningitis.

4. *The value of immune serum given intraspinally.* The value of immune serum given intraspinally has been demonstrated experimentally, showing that when injected into the spinal fluid it may prevent the invasion of the central nervous system by the virus.^{36, 2, 54, 53} Netter and Salanier¹⁰⁵ were the first to use immune serum in human cases. While the therapeutic value of the use of convalescent serum in the "passage period" of Draper²⁷ is still in question, it will, if established, be good evidence in favor of blood or lymphatic transmission of the virus.

F. *Changes in the perivascular spaces and interstitial inflammation constitute the primary lesions in the central nervous system.*—Burrows¹⁰ found that the primary changes in the nervous tissues were always in the perivascular lymphatic spaces, which became distended with fluid, and showed proliferation of the endothelial lining cells. Wickman¹³² believed the virus was carried through the lymphatics. He reported that the lymphatics, not the capillaries, were damaged first. Primary interstitial inflammation with proportional nerve cell damage has been described.^{57, 115, 11, 8, 131, 124, 60, 126} Peabody, Draper and Dochez¹¹⁰ and Flexner³³ have described a combination of mechanical forces acting to injure the nerve cell by reducing its blood supply and gaseous exchange, though both authors recognized the possibility of a combined toxic action. Amoss³ stated "A considerable part of cell damage results from a lack of gaseous interchange due to perineuronal edema. Only on this supposition can one explain the dramatic return of function in a completely paralyzed muscle within forty-eight hours." Clark and Amoss¹⁵ described meningeal inflammation without paralysis and concluded that interstitial changes played a determining part. Clark¹⁴ was able to prolong the life of his experimental animals by injecting epinephrine, presumably lessening congestion by constricting the vessels.

Summary

Flexner's view of transmission of the virus has received more widespread support than any other theory. Briefly, he believes the virus reaches the cord by passage or propagation along the lymphatics and the vascular system, thus reaching the nervous elements and because of the perivascular reaction the anterior horn cells die

of ischemia. Burrows represents the extreme view that poliomyelitis should be classed with diseases of the lymphatic system. Fairbrother and Hurst renew the concept first given by Leiner and v. Wiesner that direct toxic action on the cells antedates the generalized infiltration and perivascular cuffing found at autopsy. Researches on the blood and spinal fluid indicate that these fluids are of importance in transporting the virus from the portal of entry to the central nervous system.

PORTALS OF ENTRY

I. *Nasopharynx*

The nasopharynx as a portal of entry of the virus of poliomyelitis has received support both from those who think the virus travels along nerve fibers and from those who adhere to the theories of invasion by way of the lymphatics and the blood stream. Several points may be mentioned in favor of entrance of the virus through the nasopharynx:

A. Intranasal inoculation is one of the established methods of experimental transmission of the disease, and though irregularly effective, it has been classed second only to the intracerebral route,³⁴ and has been considered by many to be the natural route of infection in man.^{34, 56, 34a}

B. The virus has been found present:

1. Regularly in the tonsils and nasopharyngeal mucosa of human⁴³ and experimental cases.^{41, 52, 52}

2. In the nasal washings from healthy persons in contact with patients.⁴⁶

3. In the nasal washings from a girl six days before the onset of an attack of poliomyelitis.¹²⁵

C. The nasopharynx has been designated as the place of elimination of the virus, as well as its portal of entry.^{2, 34} In postmortem examination of cases of experimental poliomyelitis the virus has been found in the nasal secretions, nasal mucosa, tonsils and lymphoid tissues of the pharyngeal ring regardless of the route of inoculation.⁵²

D. A slight positive correlation between poliomyelitis and tonsillectomy in children was found by Aycock and Luther,⁶ indicating that surgical injury of the mucosa was predisposing to the infection.

II. *Gastrointestinal tract*—

The gastrointestinal tract as a portal of entry of the virus of poliomyelitis has been supported by many who believe that the virus is transmitted to the central nervous system by way of the lymphatics, by others who favor invasion by way of the blood stream, and by still others who supported the theory of axonic transmission. Ideas bearing on this question have been derived chiefly from four sources:

A. *Clinical*.—1. *Symptoms*. The onset of the disease is accompanied by gastrointestinal symptoms in 90 per cent. of cases.² Prominent among the prodromal symptoms are loss of appetite, nausea, vomiting, and constipation or diarrhea closely simulating a mild gastrointestinal upset.

2. *Predominance of paralysis in the lower limbs*. Both lower limbs are involved in 43.7 per cent. of cases, and one or both limbs in 85.4 per cent. of cases.^{132, 94}

B. *Pathological*.—1. *Gastrointestinal lesions* have frequently been described at autopsy as hyperemia and folliculitis involving the solitary follicles and Peyer's patches with ulcerations.^{98, 10}

2. *Mesenteric lymph nodes* have been reported infective in two of three cases inoculated by ingestion of the virus by mouth.³⁰ Mesenteric lymph nodes always show hyperplasia in fatal human cases.¹⁰

3. *Abdominal sympathetic ganglia* were reported to have been injured by lesions typical of the disease in an early human case brought to autopsy on the sixth day, and in monkeys inoculated by intraperitoneal injection.¹⁰⁴ Lesions were found only in the gray matter of the ganglia, not in the nerve fibers. The route of invasion described from this histopathological evidence starts from the lumen of the gut, passes to the enteric plexus of Auerbach and Meissner, by way of nerve fibers to the ganglia of the solar plexus, thence to the sympathetic trunk, through the rami communicans to the roots of the spinal nerves and into the spinal cord. Poliomyelitis in a monkey, refractory to the disease, but showing infection in a typical abortive form, gave similar pathological lesions of the sympathetics, most pronounced in the hypogastric plexus near the site of the injection, and including also the dorsal root ganglia.²⁴

C. *Experimental poliomyelitis produced by gastrointestinal in-*

oculation.—Levaditi, Kling, and Lepine⁹⁰ report that it is easy to infect cynomolgus monkeys by the gastrointestinal tract, without any previous preparation of the animals. Clark, Roberts and Preston¹⁷ report that they were able to obtain only negative results from oral administration of the virus to cynomolgus monkeys, and call attention to the point that in the report of Levaditi, Kling and Lepine no one of the three animals fed with the virus presented a typical picture of the disease, also no description of the microscopic examination was given.

Leiner and v. Wiesner⁸⁸ reported positive infection in two of five animals fed with the virus following the administration of sodium bicarbonate to reduce acidity, and morphine to lessen the intestinal motility. Amoss² reported that he was entirely unable to confirm those results. Several other investigators have reported negative results from similar experiments.^{121, 50, 18} Saddington¹¹⁷ described a vascular lesion in a monkey inoculated by the gastrointestinal tract.

Typical infection has been found to result from the injection of the virus into an intestinal loop.^{90, 88} The feces are not commonly infective following ingestion of the virus,¹⁸ but may be positive for two days following the feeding of large quantities of the emulsified cord or brain.^{90, 17} It is possible that the infective agent is attenuated by gastrointestinal passage.⁹⁰

D. Epidemiological.—Reports of milk-borne epidemics constitute one of the chief arguments in favor of the gastrointestinal entry of the virus, though this is not generally believed to be the most common means of transmission of the disease.^{4, 130, 84, 25} Kling⁶⁹ has concluded from epidemiological studies in Sweden, Saxony, and Roumania that "water is an important vehicle for the poliomyelitis germ and plays a great part in the transmission of the disease. Without water there can be no poliomyelitic foci formed." Kling failed to find any experimental proof of carriers, contrary to the numerous reports of other investigators.^{46, 95, 71} Students of this phase of the question point out that in Sweden and other countries where Kling has worked, the waterways arise in the rural districts where poliomyelitis is notoriously common. The habitable part of the land is along the waterways so that the disease must necessarily be confined to the water courses, which are also the chief routes of trade and communication.

Epidemics of gastrointestinal infections have been reported as precursors of bonafide poliomyelitis epidemics.^{88, 89} The fact that the osmotic permeability of the intestinal mucosa is increased by acute inflammation has been offered as an explanation of the mechanism by which healthy carriers may become acute cases. A number of points have been offered in support of this theory:

Most of the cases of poliomyelitis occur in the early years of life when diseases of the gastrointestinal tract have their greatest incidence. Summer epidemics correlate with the incidence of summer diarrhea in children.

When the curve of incidence has two points the winter one corresponds with that of the common cold.

The curve of incidence of poliomyelitis is almost identical with that of typhoid fever.⁸⁴ The fact that typhoid comes every year, and poliomyelitis only after long intervals of ten to fifteen years, is accounted for by the theories of widespread immunization among the population, especially in urban districts.

Summary

There is no generally accepted opinion as to the site of invasion in poliomyelitis. The most support, epidemiological and experimental, has been for the nasopharynx. Sufficient experimental evidence has been given to show that the virus can readily enter through the nasal mucous membrane. Epidemiological and immunological studies indicate contact and carrier factors in the spread of the disease. The gastrointestinal tract as a portal of entry has been much talked of recently, along with general lymphatic hyperplasia, but no very convincing evidence has been given for combining the two in a scheme of pathogenesis. The route taken by the virus on its way to the spinal cord has not been finally solved. An understanding of the mode of infection would lead to the framing of measures of prevention that, with reasonable certainty, could be expected to control the spread of the disease.

REFERENCES

- ¹ ABRAMSON, H. L.: "Does the Spinal Fluid from Human Poliomyelitis Contain the Specific Infective Agent?" *J.A.M.A.*, 58:546, 1917.
- ² AMOSS, H. L.: "Filterable Viruses," Rivers *et al.*, Williams and Wilkins, Baltimore, 1928.
- ³ AMOSS, H. L.: "Poliomyelitis," *South.M.J.*, 23:18, 1930.

- ⁴ ATCOCK, W. L.: "A Milk-borne Epidemic of Poliomyelitis," *Am.J.Hyg.*, 7:791, 1927.
- ⁵ ATCOCK, W. L.: "The Poliomyelitis Problem from the Point of View of Its Epidemiology," *California & West.Med.*, 35:249, 1931.
- ⁶ ATCOCK, W. L., AND LUTHER, E. H.: "The Occurrence of Poliomyelitis Following Tonsillectomy," *New England J.Med.*, 200:164, 1929.
- ⁷ BATTEN, F. E.: "The Pathology of Infantile Paralysis (Acute Anterior Poliomyelitis)," *Brain*, 27:376, 1904.
- ⁸ BENECKE: "Ueber poliomyelitis acuta," *München.med.Wchnschr.*, 57:176, 1910.
- ⁹ BLANTON, W. B.: "Anatomical Study of Poliomyelitis," *J.M.Res.*, 36:1, 1917.
- ¹⁰ BURROWS, M. T.: "Is Poliomyelitis a Disease of the Lymphatic System?" *Arch.Int.Med.*, 48:33, 1931.
- ¹¹ BUZZARD, E. F.: "On Certain Acute Infective or Toxic Conditions of the Nervous System," *Brain*, 30:1, 1907.
- ¹² CASSIRER, R.: "Neuere Erfahrungen uber die akute spinale Kinderlähmung," *Berl.klin.Wchnschr.*, 47:2295, 1910.
- ¹³ CHARCOT, J. A., AND JOFFROY, A.: "Cas de paralysie infantile spinale avec lesions des cornes anterieures de la substance grise de la moelle epiniere," *Arch.de physiol.norm.et path.*, 3:134, 1870.
- ¹⁴ CLARK, P. F.: "The Action of Subdural Injections of Epinephrin in Experimental Poliomyelitis," *J.A.M.A.*, 59:367, 1912.
- ¹⁵ CLARK, P. F., AND AMOSS, H. L.: "Intraspinal Infection in Experimental Poliomyelitis," *J.Exper.Med.*, 19:217, 1914.
- ¹⁶ CLARK, P. F., FRASER, F. R., AND AMOSS, H. L.: "The Relation to the Blood of the Virus of Epidemic Poliomyelitis," *J.Exper.Med.*, 19:223, 1914.
- ¹⁷ CLARK, P. F., ROBERTS, D. J., AND PRESTON, W. S., JR.: "Passage of Poliomyelitis Virus Through the Intestinal Tract," *J.Prev.Med.*, 6:47, 1932.
- ¹⁸ CLARK, P. F., SCHINDLER, D., AND ROBERTS, J.: "Properties of Poliomyelitis Virus," *J.Bact.*, 20:213, 1930.
- ¹⁹ COBB, S., AND TALBOTT, J. H.: "Studies in Cerebral Circulation: II. A Quantitative Study of Cerebral Capillaries," *Tr.Assn.Am.Phys.*, 42:255, 1927.
- ²⁰ COHNHEIM, J.: "Untersuchungen ueber die embolischen Prozesse," Berlin, Hirschwald, 1872.
- ²¹ COTUGNO, DOMENICO: "De Ischiade Nervosa," Vienna, 1770.
- ²² CUSHING, H.: "Studies in Intracranial Physiology and Surgery," Oxford Med. Pub., London, Oxford Univ. Press, 1926.
- ²³ DECHAUME, J., SEDALLIAN, P., ET MORIN, G.: "Lésions nerveuses viscerales chez un singe refractaire à la poliomyélite experimentale," *Compt.rend.Soc. de biol.*, 106:296, 1931.
- ²⁴ DINGMAN, J. C.: "Report of a Possibly Milk-borne Epidemic of Infantile Paralysis," *Med.Rec.N.Y.*, 90:922, 1916.
- ²⁵ DRAPER, G.: "Acute Poliomyelitis," Philadelphia, Blakiston, 1917.
- ²⁶ DRAPER, G.: "Significant Problems in Acute Anterior Poliomyelitis," *J.A.M.A.*, 97:1130, 1931.
- ²⁷ DRAPER, G., AND PEABODY, F. W.: "A Study of the Cerebrospinal Fluid and Blood in Acute Poliomyelitis," *Am.J.Dis.Child.*, 3:153, 1912.
- ²⁸ DYKE, C. G., AND DEERY, E. M.: "An Observation on the Relationship of the Subarachnoid and Perineural Spaces," *Bull.Neurol.Inst.New York*, 1:593, 1931.

- ³⁰ ELMAN, R.: "Spinal Arachnoid Granulations with Special Reference to the Cerebrospinal Fluid," *Bull. Johns Hopkins Hosp.*, 34:1923.
- ³¹ FABER, H. K.: "Poliomyelitis—An Essential Nerve System Disease Throughout Its Course," *Science*, 75:108, 1932.
- ³² FAIRBROTHER, R. W., AND HURST, E. W.: "The Pathogenesis of, and Propagation of the Virus in, Experimental Poliomyelitis," *J. Path. & Bact.*, 33:17, 1930.
- ³³ FLEXNER, S.: "The Contribution of Experimental to Human Poliomyelitis," *J.A.M.A.*, 55:1105, 1910.
- ³⁴ FLEXNER, S.: "Some Problems in Infection and Its Control," *Lancet*, 2:1271, 1912.
- ³⁵ FLEXNER, S.: "Prevention of Poliomyelitis," *Science*, 77:7, 1933.
- ³⁶ FLEXNER, S., AND AMOSS, H. L.: "Penetration of the Virus of Poliomyelitis from the Blood into the Cerebrospinal Fluid," *J. Exper. Med.*, 19:411, 1914.
- ³⁷ FLEXNER, S., AMOSS, H. L.: "Localization of the Virus and Pathogenesis of Epidemic Poliomyelitis," *J. Exper. Med.*, 20:249, 1914.
- ³⁸ FLEXNER, S., AND AMOSS, H. L.: "The Relation of the Meninges and Choroid Plexus to Poliomyelitic Infection," *J. Exper. Med.*, 25:525, 1917.
- ³⁹ FLEXNER, S., AND AMOSS, H. L.: "The Passage of Neutralizing Substances from the Blood into the Cerebrospinal Fluid in Poliomyelitis," *J. Exper. Med.*, 25:499, 1917.
- ⁴⁰ FLEXNER, S., AND AMOSS, H. L.: "The Passage of Neutralizing Substance from the Blood into the Cerebrospinal Fluid in Actively Immunized Monkeys," *J. Exper. Med.*, 28:11, 1918.
- ⁴¹ FLEXNER, S., AND AMOSS, H. L.: "Persistence of the Virus of Poliomyelitis in the Nasopharynx," *J. Exper. Med.*, 29:379, 1918.
- ⁴² FLEXNER, S., AND AMOSS, H. L.: "Experiments on the Nasal Route of Infection in Poliomyelitis," *J. Exper. Med.*, 31:123, 1920.
- ⁴³ FLEXNER, S., AMOSS, H. L., AND EBERSON, F.: "Physiological Stimulation of the Choroid Plexus and Experimental Poliomyelitis," *J. Exper. Med.*, 27:679, 1918.
- ⁴⁴ FLEXNER, S., AND CLARK, P. F.: "Epidemic Poliomyelitis. Eleventh Note: Relation of the Virus to the Tonsils, Blood and Cerebrospinal Fluid; Races of the Virus," *J.A.M.A.*, 57:1685, 1911.
- ⁴⁵ FLEXNER, S., CLARK, P. F., AND AMOSS, H. L.: "A Contribution to the Epidemiology of Poliomyelitis," *J. Exper. Med.*, 19:195, 1914.
- ⁴⁶ FLEXNER, S., CLARK, P. F., AND AMOSS, H. L.: "A Contribution to the Pathology of Epidemic Poliomyelitis," *J. Exper. Med.*, 19:205, 1914.
- ⁴⁷ FLEXNER, S., CLARK, P. F., AND FRASER, F. R.: "Epidemic Poliomyelitis. Fourteenth Note: Passive Human Carriage of the Virus of Poliomyelitis," *J.A.M.A.*, 60:201, 1913.
- ⁴⁸ FLEXNER, S., AND LEWIS, P. A.: "The Transmission of Acute Poliomyelitis to Monkeys," *J.A.M.A.*, 53:1639, 1909.
- ⁴⁹ FLEXNER, S., AND LEWIS, P. A.: "The Nature of the Virus of Epidemic Poliomyelitis," *J.A.M.A.*, 53:2095, 1909.
- ⁵⁰ FLEXNER, S., AND LEWIS, P. A.: "The Transmission of Epidemic Poliomyelitis to Monkeys. A Further Note," *J.A.M.A.*, 53:1913, 1909.
- ⁵¹ FLEXNER, S., AND LEWIS, P. A.: "Experimental Epidemic Poliomyelitis in Monkeys," *J. Exper. Med.*, 12:227, 1910.
- ⁵² FLEXNER, S., AND LEWIS, P. A.: "Experimental Epidemic Poliomyelitis in

- Monkeys. Sixth Note: Characteristic Alterations of the Cerebrospinal Fluid and Its Early Infectivity; Infection from Human Mesenteric Lymph Node," *J.A.M.A.*, 54:1140, 1910.
- ¹² FLEXNER, S., AND LEWIS, P. A.: "Epidemic Poliomyelitis in Monkeys. A Mode of Spontaneous Infection," *J.A.M.A.*, 54:535, 1910.
- ¹³ FLEXNER, S., AND LEWIS, P. A.: "Experimental Poliomyelitis in Monkeys. Seventh Note: Active Immunization and Passive Serum Protection," *J.A.M.A.*, 54:1780, 1910.
- ¹⁴ FLEXNER, S., AND LEWIS, P. A.: "Experimental Poliomyelitis in Monkeys. Eighth Note: Further Contributions to the Subjects of Immunization and Serum Therapy," *J.A.M.A.*, 55:602, 1910.
- ¹⁵ FLEXNER, S., AND STEWART: "Protective Action of Convalescent Poliomyelitis Serum," *J.A.M.A.*, 91:383, 1928.
- ¹⁶ GOODPASTURE, E. W.: "The Pathways of Infection of the Central Nervous System in Herpetic Encephalitis of Rabbits Contracted by Contact; with a Comparative Comment on Medullary Lesions in a Case of Human Poliomyelitis," *Am.J.Path.*, 1:29, 1925.
- ¹⁷ GOLDSCHIEDER, A.: "Ueber poliomyelitis," *Ztschr.f.klin.Med.*, 23:494, 1893.
- ¹⁸ GREENFIELD, J. G.: "Discussion on Encephalo-myelitis of Man and Animals," *Proc.Roy.Soc.Med.*, 22:1171, 1920.
- ¹⁹ HABBITZ, F., AND SCHEEL, O.: "Pathologisch-anatomische Untersuchungen über akute Poliomyelitis und verwandte Krankheiten," Christiania, Broeggers, 1907.
- ²⁰ HABBITZ, F., AND SCHEEL, O.: "Epidemic Acute Poliomyelitis in Norway in the Years 1903 to 1906," *J.A.M.A.*, 49:1420, 1907.
- ²¹ HASSIN, G. B.: "Villi of the Spinal Arachnoid," *Arch.Neurol.& Psychiat.*, 23:No. 1, 65, 1930.
- ²² HOWARD, C. W., AND CLARK, P. F.: "Experiments on Insect Transmission of the Virus of Poliomyelitis," *J.Exper.Med.*, 16:850, 1912.
- ²³ HUGHSON, W.: "The Embryogenesis of the Human Cerebrospinal Fluid: Its Sources, Circulatory Pathways and Destination, Together with Its Relation to the Blood and Lymph Vascular Systems. Section I, Chapter II, The Human Cerebrospinal Fluid," Hoeber, New York, 1920.
- ²⁴ HURST, E. W.: "The Histology of Experimental Poliomyelitis," *J.Path.& Bact.*, 32:457, 1929.
- ²⁵ HURST, E. W.: "A Further Contribution to the Pathogenesis of Experimental Poliomyelitis," *J.Path.& Bact.*, 33:1133, 1930.
- ²⁶ HURST, E. W.: "Further Observations on the Pathogenesis of Experimental Poliomyelitis: Intrathecal Inoculation of the Virus," *J.Path.& Bact.*, 35:41, 1932.
- ²⁷ JUNGBLUT, C. W., AND SPRING, W. J.: "A Note on the Propagation of the Virus in Experimental Poliomyelitis," *Proc.Soc.Exper.Biol.& Med.*, 27:1076, 1930.
- ²⁸ KEY, E. A. H., AND RETZIUS, M. G.: "Anatomie des Nervensystems und des Bindegewebe," Stockholm, P. A., Norstedt & Soner, 1876.
- ²⁹ KLING, C.: "Neuere Erfahrungen über die Ausbreitungweise der Akuten Poliomyelitis," *Acta psychiat.et neurol.*, 6:337, 1931.
- ³⁰ KLING, C., LEVADITY, C., AND LEVINE, P.: "Transmission of Poliomyelitis in Monkeys by Introduction of the Virus into the Digestive Tube," *Bull. Acad.de méd.*, Paris, 102:159, 1929.

- ⁷¹ KLING, C., PETERSSON, A., AND WERNSTEDT, W.: "Investigations on Epidemic Infantile Paralysis," Rep. State Med. Inst. Sweden to XVth Internat. Congr. Hyg. and Demography, Washington, 5:211, 1912.
- ⁷² KNAPP, A. C., GODFREY, E. S., JR., AND AYCOCK, W. L.: "An Outbreak of Poliomyelitis Apparently Milk-borne," *J.A.M.A.*, 87:635, 1926.
- ⁷³ KRAMER, S. D.: "Experimental Poliomyelitis," *Am.J.Pub.Hlth*, 22:381, 1932.
- ⁷⁴ KRAUSE, P., AND MEINICKE, E.: "Zur Aetiologie der akuten epidemischen Kinderlähmung," *Deutsch.med.Wchnschr.*, 25:1825, 1909.
- ⁷⁵ KUBIE, L. S.: "A Study of the Perivascular Tissues of the Central Nervous System, with the Supravital Technique," *J.Exper.Med.*, 46:615, 1927.
- ⁷⁶ KUBIE, L. S.: "Intracranial Pressure Changes During Forced Drainage of the Central Nervous System: the Hydration Factor," Chap. IV in: "The Intracranial Pressure in Health and Disease," Vol. VIII of Assoc. for Research in Nervous and Mental Disease. Series of Research Publications, Williams and Wilkins, Baltimore.
- ⁷⁷ LANDSTEINER, K.: "Poliomyelitis acuta," in Kolle and v. Wassermann's "Handbuch der pathogenen Mikroorganismen," Jena, Fischer, 2nd ed., 1913.
- ⁷⁸ LANDSTEINER, K., AND LEVADITI, C.: "La transmission de la paralysie infantile au singes," *Compt.rend.Soc.de biol.*, 67:592, 1909.
- ⁷⁹ LANDSTEINER, K., AND LEVADITI, C.: "La paralysie infantile experimentale. (Deuxieme note)," *Compt.rend.Soc.de biol.*, 67:787, 1909.
- ⁸⁰ LANDSTEINER, K., AND LEVADITI, C.: "Etude experimentale de la poliomyelite aigue (maladie de Heine-Medin)," *Ann.Inst.Pasteur*, 24:833, 1910.
- ⁸¹ LANDSTEINER, K., LEVADITI, C., AND DANULESCO, V.: "Présence du virus de la poliomyelite dans l'amygdale des singes paralysees et son elimination par le mucus nasal," *Compt.rend.Soc.de biol.*, 71:558, 1911.
- ⁸² LANDSTEINER, K., LEVADITI, C., AND PASTIA, M.: "Etude experimentale de la poliomyelite aigue (maladie de Heine-Medin) Second memoire," *Ann.Inst. Pasteur*, 25:804, 1911.
- ⁸³ LANDSTEINER, K., AND POPPER, E.: "Uebertragung der Poliomyelitis acuta auf Affen," *Ztschr.f.Immunitätsforsch., Orig.*, 2:377, 1909.
- ⁸⁴ League of Nations Monthly Epid. Rept., 9:45, 1930.
- ⁸⁵ LEINER, C., AND V. WIESNER, R.: "Experimentelle Untersuchungen uber Poliomyelitis acuta anterior," *Wien.klin.Wchnschr.*, 22:1698, 1909.
- ⁸⁶ LEINER, C., AND V. WIESNER, R.: "Experimentelle Untersuchungen uber Poliomyelitis acuta anterior, II," *Wien.klin.Wchnschr.*, 23:91, 1910.
- ⁸⁷ LEINER, C., AND V. WIESNER, R.: "Experimentelle Untersuchungen uber Poliomyelitis acuta anterior, III," *Wien.klin.Wchnschr.*, 23:323, 1910.
- ⁸⁸ LEINER, C., AND V. WIESNER, R.: "Experimentelle Untersuchungen uber Poliomyelitis acuta anterior, IV," *Wien.klin.Wchnschr.*, 23:817, 1910.
- ⁸⁹ LEVADITI, C., AND DANULESCO, V.: "La penetrabilite du virus de la poliomyelite a traverse la muqueuse nasale et l'action preventive des antiseptiques appliques localement," *Compt.rend.Soc.de biol.*, 73:252, 1912.
- ⁹⁰ LEVADITI, C., KLING, C., ET LEPINE, P.: "Nouvelles recherches experimentales sur la transmission de la poliomyelite par la voie digestive," *Bull.Acad.de med., Paris*, 105:190, 1931.
- ⁹¹ LEVADITI, C., LANDSTEINER, K., AND PASTIA, C.: "Recherche du virus dans les organes d'un enfant atteint de poliomyelite aigue," *Compt.rend.Acad. de sc.*, 152:1701, 1911.
- ⁹² LEVADITI, C., AND WILLEMIN, L.: "Étude de l'épidémie du poliomyélite du département du Bas-Rhin," *Ann.Inst.Pasteur*, 46:233, 1931.

- ⁶³ LORENTI DI NO, R.: "Ein Beitrag zur Kenntnis der Gefassverteilung in der Hirnrinde," *Jour.f.Psychol.u.Neurol.*, 35:19, 1927-1928.
- ⁶⁴ LOVETT, R. W., AND LUCAS, W. P.: "Infantile Paralysis, *J.A.M.A.*, 51:1677, 1908.
- ⁶⁵ LUCAS, W. P., AND OSGOOD, R. B.: "Transmission Experiments with the Virus of Poliomyelitis. Finding the Virus in the Nasal Secretion of a Human Carrier Four Months After the Acute Stage of a Second Attack of Poliomyelitis," *J.A.M.A.*, 60:1611, 1913.
- ⁶⁶ MARINESCO, G.: "De la transmission du virus de la poliomyelite par le nerf peripherique et ses rapports avec ces infections ascendantes," *Compt.rend. Soc.de biol.*, 70:286, 1911.
- ⁶⁷ MARINESCO, G., MANICATIDE, M., AND STATE-DRAGANESCO: "Etude clinico-therapeutique et anatomo-pathologique sur l'epidemie de paralysie infantile qui a servi en Roumanie pendant l'annee 1927," *Ann.Inst.Pasteur*, 43:223, 1929.
- ⁶⁸ MAYEHOFFER, E.: "Die gastroenteritische Eingangspforte der Poliomyelitis acuta anterior im fruhen Kindesalter," *Wien.Med.Wchnschr.*, 80:819, 1930.
- ⁶⁹ MONAKOW, C., AND MOURGUE, R.: "Introduction Biologique à l'Étude de la Neurologie et de la Psychopathologie," Paris, Alcan., 1928.
- ⁷⁰ MONCKEBERG, J. G.: "Anatomischer Befund eines Falles von Landry'schem Symptomenkomplex," *München med.Wchnschr.*, 1:1958, 1903.
- ⁷¹ MONEY, A.: "The Spinal Cord of Recent and Old Cases of Infantile Palsy," *Tr.Path.Soc.London*, 1884.
- ⁷² MORGAN, L. O.: "Iron Hematoxylin as a Myelin-sheath Stain and Neutral Red Ripened by Colon Bacillus as a Nerve-cell Stain," *Anat.Rec.*, 32:283, 1926.
- ⁷³ MOTT, G. W.: "Microscopical Examination of the Spinal Cord, Peripheral Nerves and Muscles in a Case of Acute Poliomyelitis. Fatal Termination Sixteen Days from the Onset," *Arch. of Neurol. from the Path. Lab. of the London County Asylums, Claybury, Essex, King and Son, Westminster, S.W.*
- ⁷⁴ MOURIQUAND, G., DICHAUME, I., SEDALLIAN, P., AND MORIN, G.: "Maladie de Heine-Medin et systeme nerveux vegetatif," *Rev.neurol.*, 1:1141, 1930.
- ⁷⁵ NETTER, A., AND SALANIER, M.: "Deux nouveaux cas de poliomyelite a debut meninge gueris par les injections intrarchidiennes de serum d'anciens malades," *Bullet mém.Soc.méd.d.hôp.de Paris*, 40:299, 1916.
- ⁷⁶ NEUSTEADTER, M., AND THRO, W. C.: "Experimental Poliomyelitis, Produced in Monkeys from the Dust of the Sickroom," *New York Med.Jour.*, 94:813, 1911.
- ⁷⁷ NICOLAU, S., NICOLAU, O. D., AND GALLOWAY, I. A.: "Etude sur les septinevrites a ultravirus neurotropes," *Ann.Inst.Pasteur*, 43:1, 1929.
- ⁷⁸ NOBECOURT, P.: "Les formes meningitiques de la maladie de Heine-Medin," *Progrès méd.*, 1:54, 1932.
- ⁷⁹ OSGOOD, R. B., AND LUCAS, W. P.: "Transmission Experiments with the Virus of Poliomyelitis. Finding the Virus in the Nasopharyngeal Mucosa of Monkeys Recovered from the Acute Stage," *J.A.M.A.*, 56:495, 1911.
- ⁸⁰ PEABODY, F. W., DRAFER, G., AND DOCHEZ, A. R.: "A Clinical Study of Acute Poliomyelitis," Monograph of the Rockefeller Inst. for Med. Res., No. 4, 1912.
- ⁸¹ PENNFELD, W.: "Cytology and Cellular Pathology of the Nervous System," Vol. II, Hoeber, New York, 1932.
- ⁸² PFEIFER, R. A.: "Die Angioarchitektonik der Grosshirnrinde," Berlin, Springer, 1928.

- ¹¹³ PUTNAM, T. J., AND SCHALTENBRAND, G.: "Untersuchungen zum Kreislauf des Liquor cerebrospinalis mit Hilfe intravenöser Fluoreszineinspritzungen," *Deutsche Ztschr.f.Nervenh.*, 96:123, 1927.
- ¹¹⁴ QUINCKE, H.: "Zur Physiologie der Cerebrospinalflüssigkeit," *Arch.f.Anat.u. Physiol.* (Dubois Raymond), 153, 1872.
- ¹¹⁵ REDLICH, E.: "Beitrag zur pathologischen Anatomie der Poliomyelitis anterior acuta infantum," *Wien.klin.Wchnschr.*, 7:287, 1894.
- ¹¹⁶ ROMER, P. H.: "Die epidemische Kinderlähmung" (Heine-Medinsche Krankheit), Berlin, Springer, 1911.
- ¹¹⁷ SADDINGTON, R. S.: "An Intravascular Lesion in Poliomyelitis Induced by Feeding in *Macacus Cynomolgus*," *Proc.Soc.Exper.Biol.& Med.*, 29:838, 1932.
- ¹¹⁸ SCHALTENBRAND, AND BAILEY: "Die perivaskuläre piaglamembran des Gehirns," *J.f.Psychol.u.Neurol.*, 35:199, 1927-1928.
- ¹¹⁹ SCHREIBER, G.: "La poliomyélite epidémique," Paris.
- ¹²⁰ SCHRODER, P.: "Myelitis und poliomyelitis," *Deutsche med.Wchnschr.*, 51: 973, 1925.
- ¹²¹ SCHULTZ, E. W.: "Infection of Monkeys with Poliomyelitis by the Gastro-intestinal Route," *Proc.Soc.Exper. Biol.& Med.*, 26:632, 1929.
- ¹²² SICARD, J. A., AND CESTAN, P.: "Etude de la traversée meningo-radiculaire au niveau du trou de conjugaison le nerf de conjugaison," *Bull.et mém.Soc. méd.d.hôp.de Paris*, (3rd Series), 715, 1904.
- ¹²³ STRAUSS, I., AND HUNTOON, F. M.: "Experimental Studies on the Aetiology of Acute Poliomyelitis," *New York Med.Jour.*, 91:64, 1910.
- ¹²⁴ STRAUSS, I.: *Nerv. and Ment. Dis. Monograph series*, No. 6, New York. 1910.
- ¹²⁵ TAYLOR, E., AND AMOSS, H. L.: "Carriage of the Virus of Poliomyelitis, with Subsequent Development of the Infection," *J.Exper.Med.*, 26:745, 1917.
- ¹²⁶ WALTER, R.: "Zur Histopathologie der akuten Poliomyelitis," *Deutsche Ztschr.f.Nervenh.*, 45:79, 1912.
- ¹²⁷ WEED, L. H.: "Studies on Cerebrospinal Fluid," *J.Med.Research*, 31:1914-1915.
- ¹²⁸ WEED, L. H.: "The Absorption of Cerebrospinal Fluid into the Venous System," *Am.J.Anat.*, 31:3, 1923.
- ¹²⁹ WICKMAN, I.: "Studien über poliomyelitis acuta," *Arb.a.d.path.Inst.zu Helsingfors.*, I, 1905, also separately Berlin, 1905.
- ¹³⁰ WICKMAN, I.: "Beiträge zur Kenntnis der Heine Medinsche Krankheit," Berlin, Krager, 1907.
- ¹³¹ WICKMAN, I.: "Die akute poliomyelitis bzw. Heine-Medinsche Krankheit," in Lewandowsky's "Handbuch der Neurologie," Berlin, Springer, 1911.
- ¹³² WICKMAN, I.: "Acute Poliomyelitis (Heine-Medin's Disease)," tr. by J. W. J. A. M. Malloney, *Nervous and Mental Disease Monograph Series*, No. 10, New York, J. Nerv. and Ment. Dis. Pub. Co. 1913.
- ¹³³ ZAPPERT, J.: Heine-Medinsche Krankheit, Verhandl. 82 Versamml. Gesellsch. deut. Naturforsch. u. Aerzte Königsberg, 1910, Leipzig.
- ¹³⁴ ZAPPERT, J., v. WIESNER, R., AND LEINER, K.: "Studien über die Heine-Medinsche Krankheit," Leipzig and Vienna.
- ¹³⁵ RIVERS, T. M.: "Relation of Filterable Viruses to Diseases of the Nervous System," *Arch.Neurol. and Psychiat.*, 28:757, 1932.
- ¹³⁶ MARINESCO, G., AND DRAGANESCO, S.: "Researches on the Pathology of Certain Encephalomyelitides Due to Viruses," *Rev.Neurol.*, 1:1, 1932.

HEREDOFAMILIAL ANGIOMATOSIS (TELANGIECTASIA) WITH RECURRING HEMORRHAGES*

(Nonhemophilic, Nonpurpuric and Nonthrombopathic)
A Bibliography

By HYMAN I. GOLDSTEIN, M.D.

Fellow of the American Medical Editors' and Authors' Association;
Associate of the American College of Physicians;
Camden, New Jersey

NONHEMOPHILIC, nonpurpuric, and nonthrombopathic heredofamilial bleeding with or without (telangiectasia) heredofamilial angiomas (Rendu-Osler-Weber's Disease or Goldstein's Disease), hemophilia, thrombasthenic and thrombopenic purpura, Frank's pseudohemophilia hepatica ("hypoleukia splenicohepatica") and hemorrhagic capillary toxicosis, Von Willebrand's hepatogenic hemorrhagic diathesis, Jürgen and Von Willebrand's constitutional thrombopathy, David's hemorrhagic (dysendocrinism) disease in women, metropathia haemorrhagica, Glanzmann's familial thrombasthenic purpura, pseudohemophilia, and Biermer's hyperchromic macrocytic anemia, severe hypochromic microcytic anemia have, during recent years, received considerable attention. Recent medical literature contains many contributions concerning these various hemorrhagic and anemic blood disorders, which have not infrequently confused the clinician, pediatrician, gynecologist, and surgeon.

Reports of a conflicting nature have appeared concerning the several forms of hemorrhagic disease.

In this paper will be discussed the condition known as multiple hereditary telangiectasia with familial epistaxis, Goldstein's heredofamilial angiomas with nonthrombopathic, nonhemophilic, and nonpurpuric hemorrhages or Rendu-Osler-Weber's Disease.

A number of interesting reports of such cases have recently been published by J. F. Madden (St. Paul, 1934), I. N. Kugelmass (N. Y., 1934), Karl M. Houser (Phila., 1934), F. Földvári (Budapest, 1933), P. Mounier-Kuhn (Lyon, 1933), Karl Ullmann (Vi-

* Read before the American Hungarian Medical Association, at the New York Academy of Medicine, N. Y. City, May 4th, 1933.

enna, 1933), Gordon R. Scarff (Bristol, Eng., 1933), C. H. Aubertin, R. Lévy and Mme. Baclesse (Paris, 1933), Torrigiani (Jan. 1933), E. Wittkower and B. Rarey (Berlin, 1933), Rosenthal and Unna (Hamburg, 1933), W. Richter (Berlin, 1933), Jacob Braun (N. Y., 1933), G. Jamieson Meikle (London, 1933), E. A. Cockayne (London, 1933), Ch. Aubertin and Georges See (Paris, 1933), Fred Wise (N. Y., 1932), N. C. Wetzel (Cleveland, 1932), W. Milbradt (Jena, 1932), H. W. Gordon (London, 1932), Trow (Toronto, 1932), F. Blumenthal (Berlin, 1932), F. Rosenthal (Hamburg, 1932), Larrabee and Littman (Boston, 1932), Lagèze and Mounier-Kuhn (1932), G. Dreyfus (Paris, 1932), K. Gotsch (Prague, 1932), Hurst, Hampson, and Plummer (London, 1932), H. I. Goldstein (1931, 1932, 1933), Weisbrum and S. Neumark (Łódź, 1932), A. M. H. Gray (London, 1932), R. H. Major (Kansas City, 1932), Gutmann (1932), Paul Unna, Jr. (Hamburg, 1932), the late Leo Kessel (N. Y., 1931, 1932), H. Schmitt (1931), Aubertin and Lévy (1931), A. Reiniger (Vienna, 1931), K. Ullmann (Vienna, 1931), T. FitzHugh, Jr. (Phila., 1931), Hicks and Knox (N. Y., 1931), C. W. Bottema (1930), Földvári (Budapest, 1930), Kenedy (Budapest, 1930), L. N. Boston (Phila., 1930), R. Schoen (Leipzig, 1930), Ersner (Phila., 1930), H. Curschmann (Rostock, 1930), Van Gilse (1920), Harper (1929), F. Curtius (Bonn, 1928), Kufs (1928), Stryker (1927), Stillians (1925), Newcomet (Phila., 1925), G. Pfahler (Phila., 1925), and many others.

A number of instances of heredofamilial bleeding (*epistaxis*, etc.) have been reported which, perhaps correctly, may be included in the group of cases of "heredofamilial bleeding with or without telangiectasia or angiomatosis." Among cases reported by J. C. Scal (N. Y. 1932), E. Wordley (Plymouth, F series reported by Strauss, Globus and which are similar to those previous Elsaesser (1864), Frank (1840), (1864), (1865), Fröh Eales (1896), il (1894), (00), Kenn Bramwell n (1907). (1925), Bl. Giffin (

ay be mentioned the
ugh Garla eeds,
, Case X he
(N. Y.,),
y Ford ,
(184
enat
J.

(Hamburg, 1930), L. J. Witts' family III (Guy's Hosp. Reports, Oct. 1932, London), and Barford's cases, family IV in Witts' paper. G. Richelot reported "A Very Grave Case of Epistaxis During Pregnancy" in a primipara, aged twenty-eight years, who had been troubled with nosebleeds since the age of seven. Her father and twin brother were affected in the same manner from infancy. Richelot prescribed iron for her in 1839, when he first saw her (aged twenty-five years).

Madden, erroneously, states that Sutton, in 1864, first reported hereditary hemorrhagic telangiectasia "as internal hemorrhages and telangiectasia of the skin" and that "Chiari, in 1833, regarded it as hemophilia of slight degree." Fordyce, in 1784, J. P. Frank, in 1840, Richelot, in 1847, Sutton, in 1864, Babington, in 1865, J. W. Legg, of London, in 1876, reported the earliest cases of this type of bleeding. Madden overlooked entirely the reports by Legg, Verneuil, Fröhlich, and Senator, and a number of others. The cases recorded by Legg, Chiari, Senator, and Rendu, of Paris (1896), were typical examples of the clinical entity discussed in this paper, and which the writer first named "Rendu-Osler-Weber's Disease" (1930), now known as "heredofamilial angiomatosis." The cases as reported by Sutton (1864), and Babington (1865), were instances of familial epistaxis. Telangiectases of the heredofamilial type may or may not have been present in these cases, but no mention is made of them. Osler, in his third and final paper on the subject, in the *Riforma Medica*, in 1911, however, stated that Babington's cases undoubtedly belonged in this group.

It is of interest to note, here, that Hans Kufs, in 1928, reported an instance of an eighty-one year old man with multiple cerebral telangiectases in the brain, as the explanation for the cerebral condition from which his forty-three year old daughter had been suffering for twenty-six years (facial paralysis, paresthesia, tinnitus aurium, diplopia, all without progression). The daughter was believed to have had hemorrhages from similar telangiectases. In this connection I may mention my first case in a woman forty-two years of age who had cerebral hemorrhages undoubtedly telangiectatic in origin. Eleven members in her family suffered from repeated nosebleed and telangiectases. These cases were first reported by me in the *Archives of Internal Medicine*, January 15, 1921. Mention

should also be made here of Victor Levine's paper on "Angiomatous Malformations of the Brain" (March 1933), and the papers by Strauss, Globus and Ginsburg (May 1932), R. C. Larrabee and D. Littman (Dec. 29, 1932), H. Uiberall (Vienna, 1930), and the monograph by Professor E. Frank, Breslau, on "Hämorrhagische Diathesen," which appeared in the *Neuen Deutschen Klinik*, Band IV, Lieferung 18, 1929, pp. 395-437.

Kugelmass, of New York, in his special article on "Clinical Control of Chronic Hemorrhagic States in Childhood," which appeared in the *Journal of The American Medical Association* (Jan. 1934), on page 291, reports an instance of hereditary hemorrhagic telangiectasis in a girl aged thirteen years, a twin, who suffered from repeated nosebleeds. The other twin was normal, but the grandmother, paternal uncle and nephew had similar attacks. Examination of the blood showed hemoglobin, 60 per cent; red blood cells, 4,000,000; white blood cells, 8,500; polymorphonuclears, 65 per cent; platelets, 280,000; clotting time, three minutes; bleeding time, five minutes; clot retraction, three hours; tourniquet test, negative. Examination of the nasal and mucous membranes showed multiple angiomata as the local cause for bleeding. Kugelmass states that puberty first precipitates bleeding varicosities which characterize this developmental effect.

In 1916 Hess described a third hereditary haemorrhagic diathesis, which was a hereditary form of purpura haemorrhagica. This condition must not be confused with the definite clinical entity under discussion in this paper.

Willebrand, of Helsingfors, and Jürgens, of Leipzig, (March 18, 1933) under the title of "Über Eine Neue Bluterkrankheit, Die Konstitutionelle Thrombopathie" discussed what they considered a new hemorrhagic entity called "Constitutional Thrombopathy".

Madden, of St. Paul (Feb. 10, 1934) reported a case of hereditary hemorrhagic telangiectasia illustrating the primary type of generalized angiomatosis in a woman aged sixty-four, first seen in the dermatologic department because of lesions on the skin and tongue. The eruption had been present as long as she could remember. New lesions appeared from time to time, but none had disappeared. The eruption was generalized, but there were only a few

scattered lesions below the neck. The lesions were located particularly on the face and mucous membranes of the nose and mouth. The telangiectasias became more numerous near the midline of the face and were most marked on the nose, lips and malar eminences. There was an extensive telangiectatic network covering the nasal septum. Both sides of the nasal septum were almost covered with telangiectasias. The patient had complained of severe nosebleeds at frequent intervals for years. The hemorrhages seemed to start spontaneously and often lasted for from fifteen minutes to an hour. There were times when she had from ten to fifteen nasal hemorrhages in one day. The bleeding usually stopped spontaneously or on the application of pressure. It was never necessary to call a physician to stop a hemorrhage. The epistaxis had become more frequent in recent years.

Gutmann, Laval, and Schlumberger, of Paris, discussed "Hemorragies digestives chez un angiomeux" (Seance du 28, Janvier 1932)—Bull. et Mem. de la Societe Med. des Hop. de Paris February 8, 1932. P. Chevallier, à Cochin, spoke of "Petite hemophilohemogenie". In the discussion, P. Emile-Weil mentioned his own paper in *le Sang*, No. 1, 1927, "Etude sur les angiomeux".

Robert Bachrach, of O. Zuckerkandl's Surgical Clinic, Vienna, published his article "Ueber Teleangiectasien der Harnblase" in *Folia Urologica*, Vol. IV, No. 2, pp. 101-106, 1909-10 (with colored plate). G. Cirio discussed "Multiple Angiomas of the Bladder and Kidney", in the *Riforma Medica* (Naples) April 22, 1933.

B. Reading reports an interesting case of congenital telangiectasis of the lung complicated by brain abscess (Nov. 1932).

E. A. Cockayne, of the Middlesex Hospital, London, in his new book "Inherited Abnormalities of the Skin and Its Appendages" (Oxford University Press, London, 1933), Chapter IV, pp. 111-117, under the heading of "Errors of Development of Elastic Tissue", discusses hereditary telangiectases. He tabulates many of the previously reported cases, omitting some of the recorded instances which I previously collected and published (1921, 1930, 1931, 1932, 1933). Of interest, is Cockayne's statement that "Horses also suffer from a similar defect of the blood-vessels which causes recurrent attacks of epistaxis and is inherited as a recessive. 'Herod', 1748, is the first racehorse known to have had it, but since his time it has

affected many others, including 'Hermit', 'Gallinule', and 'Humorist'. Crew and Buchanan Smith and Robertson give further information about its incidence in blood-stock".

Meikle, House Physician of the London Middlesex Hospital, reported his case in the London Lancet, October 14, 1933.

Mention should be made that Cockayne reports a case and in his patient telangiectases were present on the membrana tympani of both ears and in the larynx. Meikle's patient, (a man aged thirty-seven years), in addition to telangiectases on the lips, tongue, palate, nasal mucosa, finger tips and under the nails, also had telangiectases on the tympanic membrane and on the posterior wall of the external auditory canal (meatus). The man had a café-au-lait color, and suffered from epistaxis since he was twenty-one years old. The telangiectases occurred in three generations.

J. Hutchinson reported an "Almost Fatal Epistaxis in A Pregnant Woman" and mentions an instance of familial epistaxis in this report.

Von Broich, of Elberfeld, reported a case of a woman aged thirty-one years, seven weeks pregnant, who had had epistaxis as a child. She had nosebleeds every three or four days. One brother, aged forty years, had epistaxis in youth, one sister, aged thirty-eight years, was a severe bleeder, one sister, aged thirty-six years, had nosebleeds. He speaks of "Am rechten unterschenkel zahlreiche punktformige Hautblutungen, Lippen und Schleimhaute ausserst blutarm".

Abraham Strauss, of Cleveland (1933), discusses "Epistaxis in Pregnancy Requiring Ligation of the External Carotid".

The earliest reported cases of this clinical entity were erroneously considered as "hemophilia," "pseudohemophilia," and "eruptive angiomata". Cases have been reported under the title "familial epistaxis."

Legg (1843-1921) in 1876, Ottokar Chiari (1853-1918) in 1887, H. Senator (1834-1911) in 1891, H. L. J. M. Rendu (1844-1902) in 1896, Coe in 1896, K. Ullmann in 1896 and 1900, and the instances reported by Smith (1898), Osler (1901, 1907), Josserand (1902), Kennan (1902), Kelly (1906), Hawthorne (1906) and F. P. Weber (1907) are among the earliest recorded cases.

Of interest, too, are the cases reported by Sabatier (1888),

Schede (1889), Attlee (1901), Guthrie (1902), Pearson (1904), Aitken (1909), and Foggie (May 1928).

One might, perhaps, be justified in including in this group the cases reported by J. P. Frank (1840), Richelot (1847), Sutton (1864), Babington (1865), E. Wilson (1869), M. Anderson (1891), Gaston (1894), Chauffard (1896), and T. C. Fox (1908). Osler, in 1911, (*Riforma Med.* 27: 57-58, 1911) said "it is almost certain that cases of *epistaxis* recurring in five generations as referred to by Babington (*Lancet*, Sept. 23, 1865) belong to this group".

Richter's case (1933) of hereditary hemorrhagic telangiectasia may be questioned. The patient was a woman, aged twenty-seven years. There was no other similar case in the family. She suffered from some psychic shock, Basedow's disease, amyotrophic lateral sclerosis and a trophic ulcer. Hemorrhages are not mentioned.

Milbradt's (1932) case also appears to be an isolated instance, as does one of the reported cases by Wittkower (1933).

There are about 120 families recorded in medical literature and about 700 individuals suffering from this clinical entity.

DIAGNOSIS

This heredofamilial hemorrhagic disease is transmitted by both sexes. It is not sexbound—males and females bleed and have telangiectases. Hemorrhages usually occur from the nose, but may occur from the stomach, bowels, kidneys, lungs, and birth-canal. Cerebral hemorrhages have been reported.

The blood cellular elements are normal. Blood chemistry, bleeding and clotting times, platelets, calcium, etc. are normal. Secondary anemia, as the result of persistent severe hemorrhages, of course, occurs. Late in the disease, *splenomegaly* and *hepatomegaly* are sometimes in evidence, as reported by Osler, FitzHugh, Goldstein, Rosenthal, Giffin, Schoen, Roles, Curschmann, Milbradt, and others. The telangiectases are usually found on the face, nasal septum, lips, tongue, palate, under the finger nails, and on other parts of the body.

The *differential diagnosis* must be made from hemophilia, pseudo-hemophilia, Willebrand and Jürgen's "constitutional thrombopathy", Banti's Disease, David's hemorrhagic disease in women due to de-

iciency of ovarian hormones, Frank's hemorrhagic capillary toxicosis and pseudohemophilia hepatica,* familial hemorrhagic purpura, Glanzmann's thrombasthenic purpura, thrombopenic purpura hemorrhagica (Lusitanus, Riverius, Werlhof), or Rayer's hemacelinosis, afibrinogenia (Opitz and Frei, 1921), Weil's (1930) hemotrypsie hémorrhagipare, Lindau's Disease, Witts' anemia, Biermer's Disease (hyperchromic macrocytic anemia), hypochromic microcytic anemia, Bernuth's pseudohemophilia or anemia, hemogenia, hepatic cirrhosis, malignancy, and avitaminosis, atypical cases of Hodgkin's disease, and leukemic and aleukemic conditions associated with hemorrhages and telangiectases.

TREATMENT

The treatment of Goldstein's heredofamilial angiomatosis with recurring hemorrhages (Rendu-Osler-Weber's Disease or Goldstein's Disease) is limited chiefly to the control of the hemorrhages and improvement of the resulting anemia.

Submucous resection, radium, electric needle, carbon dioxide snow, roentgen ray, chromic acid bead, silver nitrate, and many other local remedies have been advised and recommended for the control of the very severe and oftentimes dangerous attacks of epistaxis from small telangiectatic lesions. Roentgen ray treatment over the bleeding areas, over the spleen and liver have been recommended. In some uncontrollable cases, ligation of the external carotid, and splenectomy have been urged as a treatment of last resort. Blood transfusions, frequently repeated, liver by mouth and by injections, fish liver, horse liver extract, liver fraction G of Cohn, autolyzed liver extract, hepaventrat, hepatrat, vegex, bemax, marmite, Lilly's extralin, "Addisonin" or "Biermerin", gastric antianemic principle, hæmopoietin, hog stomach preparations, ventriculin with iron and copper, mucotrat, stomopson, large doses of iron and arsenic, have all been used for the control of the anemia.

Injections of female sex hormones, progynon, theelin, thelestrin,

* *Frank's pseudohemophilia hepatica*—hemorrhages due to deficiency of fibrinogen, phosphorous and chloroform poisoning, acute yellow atrophy of liver, hypertrophic cirrhosis of the liver, and in chronic myelocytic leukemia hemorrhages may occur due to fibrinogen defect. The coagulation time is prolonged. There is no disturbance of blood platelets (thrombocytes) or kinetocytes.

and menformon, ovarian preparations by mouth and by injections, and the use of tissue fibrinogen, brain extract, reticulo-endothelial and thrombocytic extracts, parathormone injections, calglucon, selvadine, afenil, calcium chloride given intravenously and calcium lactate and gluconate or chloride given by mouth may be mentioned for the treatment of the hemorrhages.

Bothropic antivenin, moccasin venom (1:3000), Congo red solution, stryphnon (methylamino-aceto-orthodioxo-benzolhydrochloride), clauden, hogspleen solution, intradermal injections of animal serum, etc. have all been recommended and tried.

Harald v. Samson—Himmelstjerna, formerly of Reval, Esthonia, now of Kadrinjaam (Medical Journal and Record, Sept. 15, 1926, pp. 329-332) discussed the *oral use of ovarian hormones and implantation of ovary* in the treatment of hemophilic hemorrhages; Lachlan Grant (Lancet 2: 1279, 1904) advised the use of ovary tablets in the treatment of these hemorrhages.

C. L. Birch, A. A. Bird, and others have treated hemophiliacs with ovarian preparations. Birch states the prolongation of the coagulation time in hemophilia is due to increase in the resistance of the blood platelets. The blood is morphologically normal. She studied thirty-five cases of hemophilia. *Ovarian* therapy brought about general improvement.

Himmelstjerna (1926) states: "there is also another possibility of forcing this sinister disease (*hemophilia*) into the circle of diseases that are definitely amenable therapeutically. From time immemorial, the remarkable fact has been noted that the women of bleeder families have remained free from this disease throughout their life, but that their sons are afflicted with it with great regularity. Recent investigations, however, have shown that certain anomalies (resistance of the red blood corpuscles, an increased chlorin content, and the absence of trypanocidal substance) are demonstrable in the blood of women in bleeder families, but a manifestation of the disease, as characterized by hemorrhages that threaten life, have never, or, to be more careful, almost never been observed. This circumstance leads to the conclusion that the female body has at its disposal very powerful protective bodies, which prevent a manifestation of the disease, that is, make the formation of conserving substance impossible. This thought led me to attempting

some experiments on the influencing of the organism of bleeders by ovarian hormones, and thereby, to a certain extent, to produce the condition of an artificial hermaphroditism. At first I wanted to attempt it with a peroral administration of ovarian hormones, but with their failure there still remained *the implantation of an ovary*. At my request chemical houses manufactured an ovarian preparation by most careful methods, which contained all the hormones of the ovary of the cow. I selected this animal because hemophilia has been observed in cattle and I therefore hoped to find in them a specially effective preparation."

I. Snapper (1932), F. Wibaut, P. Niehans (1928 and 1930), E. Bartarelli (1932), R. Fiessly (1929 and 1930), L. A. Barinstein, of Odessa (Nov. 10, 1926 and Oct. 11, 1928), K. Hynek of Prague (1923, 1926), and others have made interesting contributions to the study of these hemorrhagic (hemophilic) *sex-bound* conditions.

REFERENCES

- AUBERTIN, C., AND LÉVY, R.: "Hem. Familial Angiomatosis," *Bull. et mém. Soc. méd. d. hôp. de Paris*, 47:1327-1332, 1931.
- AYRES, S., JR., BURROWS, L. A., AND ANDERSON, N. P.: "Generalized Telangiectasia and Sinus Infection; Case Cured by Treatment of Chronic Sinusitis," *Arch. Dermat. & Syph.*, 26:56-59, 1932.
- BACHRACH, ROBERT: "Ueber Teleangiektasien der Harnblase," *Folia Urologica*, 4:101-106, 1909-1910. (Colored plate.)
- BARINSTEIN, L. A.: "Zur Pathogenese der Hämophilie und der Thrombopenie," *Arch. f. klin. Chir.*, 147:749-764, 1927.
- BARRETT, J. W., AND ORR, W. F.: "Two Cases of Epistaxis, in Which Ligation of External Carotid Artery Became Necessary," *Intercolon. M. J. Australas.*, 13: 314, 1908.
- BARRIERE, VAZQUEZ A.: "Lindau's Disease, von Hippel's Disease and Coats' Retinitis," *Arch. de oftal. hispano-am.*, 31:425-455, 1931.
- BARTARELLI, E.: "La terapia ovarica dell'emofilia e una rivendicazione italiana," *Polislinico*, 39:1989, 1932.
- BIRCH, C. L.: *J. A. M. A.*, 99:1566-1572, 1932; also *J. A. M. A.*, 97:244, 1931.
- BIRD, A. A.: *California & West. Med.*, 37:318, 1932.
- BLOCH, B.: "Endocrine Form of Essential Telangiectasia, etc.," *Kongr. Schweiz. Dermat. Ven.*, June 28, 29, 1927; *Ref. Zentralbl. Hautkrkh.*, 28:247.
- BLUMENTHAL, F.: "Osler'sche Krankheit," *Zentralbl. f. Haut- u. Geschlechtskr.*, 41: 191-192, 1932.
- BLUMENTHAL, F.: "Osler'sche Krankheit," *Dermat. Wchnschr.*, 95:992-993, 1932.
- BORCHGREVNIK, J.: "A Case of Angiomatosis; Fatal Hemorrhage from the Intestinal Canal," *Norsk mag. f. lægevidensk.*, Kristiania, 5, R., 15:552-559, 1917.
- COLLIER, W. T.: "Lindau's Disease—Two Cases," *Brit. M. J.*, 2:144-145, 1931.

- CURTJUS, F. *Klin.Wchnschr.*, 7:2141-2146, 1928. (Two of this family died from bleeding.)
- DAVID, W.: "Hemorrhagic Disease in Women Due to Ovarian Hormone Deficiency," *Mcd.Klin.*, 22:1755, 1926.
- DREXFUS, G.: "Familial Hemorrhagic Angiomatosis—Case," *Hôpital*, 20:85-86, 1932.
- EDITORIAL: "Unusual Bleeding," *J.A.M.A.*, 100:839, 1933.
- EDITORIAL: *Edinburgh M.J.*, 39:738, 1932.
- FALKOWSKI, A.: "Ueber eigenartige mesenchymale Hämartome in Leber und Milz neben multiplen eruptiven Angiomen der Haut bei einem Säugling," *Beitr.z.path.Anat.u.z.allg.Path.*, 62:385-414, Jena, 1913-1914.
- FAYRE, M., AND MONNIER, J. R.: "Relations between Cutaneous Angiomas and Sclerosis of Liver," *J.de méd.de Lyon*, 12:309-312, 1931.
- FEISSLY, R., AND CURCHON, H.: *Rev.méd.de la Suisse Rom.*, 45:868-870, 1925.
- FRANK: "Hemorrhagic Capillary Toxicosis," *Enziklopædie der klin.Med.* (A. Schittenhelm), J. Springer, Berlin, Part II, 451, 1925. ("Die hämorrhagischen Diathesen in Handbuch der Krankheiten des Blutes u. d. blutbildenen Organe.")
- GARLAND, H. G.: *Lancet*, 2:1406, 1932.
- GOLDSTEIN, H. I.: *Arch.Int.Mcd.*, 27:102, 1921.
- GOLDSTEIN, H. I.: "Hereditary Epistaxis," *INTERNATIONAL CLINICS*, 3:148, 1930; 253, 1930.
- GOLDSTEIN, H. I.: "Heredofamilial Angiomatosis," *J.A.M.A.*, 97:1310, 1931.
- GOLDSTEIN, H. I.: "Rendu-Osler-Weber's Disease," *J.A.M.A.*, 97:887, 1931.
- GOLDSTEIN, H. I.: "Goldstein's Heredofamilial Angiomatosis," *Arch.Int.Mcd.*, 48: 836-865, 1931.
- GOLDSTEIN, H. I.: "Goldstein's Heredofamilial Angiomatosis," *Arch.Dermat.& Syph.*, 25:707, 1932.
- GOLDSTEIN, H. I.: "Hereditary Multiple Telangiectasia," *Arch.Dermat.& Syph.*, 26: 282-308, 1932.
- GOLDSTEIN, H. I.: "Heredofamilial Angiomatosis" (Rendu-Osler-Weber's Disease), *Tr.Am.Therap.Soc.*, 32:47-64, 1932.
- GOLDSTEIN, H. I.: "Epistaxis without Telangiectasia," *Lancet*, 1:116, 1933.
- GOLDSTEIN, H. I.: "Heredofamilial Angiomatosis," *Delaware State M.J.*, 3:161, 1931.
- GOLDSTEIN, H. I.: "Goldstein's Disease or Rendu-Osler-Weber's Disease," *Acta Dermat.-Venereol.* Vol. 13:661-694, 1932.
- GOLDSTEIN AND GOLDSTEIN: "Kinetocytes," *Delaware State M.J.*, 4:5, 1932.
- GOLDSTEIN, H. I.: "Goldstein's Heredofamilial Bleeding," *J.A.M.A.*, 100:1453, 1933.
- GORDON, H. W.: "Telangiectasia," *Proc.Roy.Soc.Med.*, 25:1552, 1932.
- GORDON, H. W.: "Osler's Telangiectasia," *Brit.J.Dermat.*, 44:503-504, 1932.
- GOTSCH, K.: "Morbus Osler," *Deutsch.med.Wchnschr.*, 58:642, 1932.
- GREY, HARRIS: "Hered. Hem. Telangiectasia," *Arch.Dermat.& Syph.*, 25:177, 1932.
- GUTTMANN, LAVAL, AND SCHLUMBERGER: "Case (Angioma) with Hemorrhages of Digestive Tract," *Bull.et mém.Soc.Méd.d.hôp.de Paris*, 48:151-154, 1932.
- HEYDE, F. T.: "Ligation of Carotid Artery for Control of Idiopathic Nasal Hemorrhage," *Laryngoscope*, 35:899, 1925.

- HURST, A. F., HAMPSON, PLUMBER, AND YATES: *Guy's Hosp.Rep.*, 82:81-87, 1932.
- JACKSON, CHEVALIER: "Ligation of External Carotid Artery Thirty-eight Times without Any Mortality," *Am.Laryngol.Assoc.*, 29:14, 1907.
- JUNIUS, P.: "Clinical Picture of Coats' Retinitis, Leber's Retinal Regeneration with Multiple Aneurysms, and Czermak's Retinal Angiomatosis," *Ztschr.f. Augenh.*, 68:207-221, 1920.
- KESSEL, LEO: "Bleeding of Benign Origin," *Tr.Sect.Practice Med.,A.M.A.*, 146-152, 1931.
- LEVINE, VICTOR: "Angiomatous Malformations of the Brain—Report of Two Cases of Angioma Racemosum," *Arch.Path.*, 15:340-351, 1933.
- LITTLE, W. D., AND AYRES, WENDELL W.: "Hemorrhagic Disease—Familial Bleeding, Tendency of Unusual Type with Splenomegaly, Affecting and Transmitted by Both Males and Females," *J.A.M.A.*, 91:1251-1252, 1928.
- MILBRADT, W.: *Arch.f.Dermat.u.Syph.*, 166:34-40, 1932.
- MILBRADT, W.: "Osler's Disease," *Dermat.Wchnschr.*, 95:1693, 1932.
- MILBRADT, W.: *Zentralbl.f.Haut- u.Geschlechtskr.*, 43:446, 1933.
- MINOT, G. R.: "A Familial Hemorrhagic Condition Associated with Prolongation of the Bleeding Time," *Am.J.M.Sc.*, 175:301, 1928.
- MÖLLER, H. U.: "Familial Angiomatosis retinae et cerebelli—Lindau's Disease," *Acta ophth.*, 7:244-260, 1929.
- MÖLLER, H. U.: "Familial Angiomatosis of Retina and Cerebellum (Lindau's Disease)," *Ugesk.f.læger*, 92:379-384, 1930.
- NAGY, G.: *Ztschr.f.klin.Med.*, 102:284, 1925.
- NEWCOMET, W. S.: "Hemophilia and Multiple Angiomas," *Arch.Dermat.& Syph.*, 11:693, 1925.
- NIEHANS, P.: *Schweiz.med.Wohnschr.*, 58:1052, 1928. (Treatment of Hemophilia.)
- NIEHANS, P.: *Schweiz. med.Wohnschr.*, 60:18-19, 1930.
- NOBECOURT, P., LIEGE, R., AND GRODNITSKY: "Immediate Stopping of Epistaxis After Splenectomy in Hemogenia—(Girl 11½ Years Old)," *Bull.Soc.de pediat.de Paris*, 30:186-194, 1932.
- PAUL, N. S.: "Hered. Telangiectases with Epistaxis," *Brit.J.Dermat.*, 30:27-32, 1918.
- PFÄHLER, G. E.: *Arch.Dermat.& Syph.*, 11:694, 1925.
- RICHELOT, G.: "Note sur un cas Très Grave D'Épistaxis Pendant la Grossesse," *L'Union Médicale*, 1:179-180, 1847.
- RICHTER, W.: "Teleangiektasia haemorrhagica hereditaria in Verbindung mit Basedow amyotrophischer Lateralsklerose," *Zentralbl.f.Haut-u.Geschlechtskr.*, 43:616, 1933.
- ROSENTHAL: "Osler'sche Krankheit," *Zentralbl.f.Haut-u.Geschlechtskr.*, 40:720-721, 1932.
- ROSENTHAL: "Osler'sche Krankheit," *Zentralbl.f.inn.Med.*, 53:787-788, 1932.
- ROSKAM, J.: "Hemogenic Type of Hemorrhagiparous Conditions; Pathogenesis and Therapy," *Scalpel*, 85:889-902, 1932.
- ROUSSY, G., AND OBERLING, C.: "Angiomatous Tumors of the Nerve Centers," *Presse méd.*, 38:179, 1930.
- SCAL, J. C.: *Med.J.& Rec.*, 136:336-337, 1932.

- SCHMITT, H.: "Question of Heredity, Diagnosis and Therapy of Osler's Hereditary Hemorrhagic Telangiectasia," *Ztschr.f.Laryng.Rhin.,Otol.*, 22:23-30, 1931.
- SCHWARTZ, F. F.: "Female Sex Hormone in Epistaxis," *Clin.Med.and Surg.*, 40: 111, 1933.
- SNAPPER, I.: *Klin. Wchnschr.*, 11:1005, 1932.
- STILLIANS, A. W.: "Familial Telangiectasia," *Arch.Dermat.&Syph.*, 12:568, 1925.
- STRAUSS, L., GLOBUS, AND GINSBURG: *Arch.Neurol.& Psychiat.*, 27:1080-1130, 1932, Case 13.
- STRYKER, G. V.: "Hered. Hem. Telangiectasia," *Arch.Dermat.& Syph.*, 15:2, 1927.
- WEIL-EMILE, P., AND ISCH-WALL, P.: "Angioma and Hemogenia," *Bull.et mem. Soc.méd.d.hôp.de Paris*, 54:1278-1282, 1930.
- WERTHEIM, LEO: "Hämangiome—(Geschwülste der Haut) Teleangiectasis seu angiomatosis hereditaria haemorrhagica, Morbus Osler, Goldstein's Heredo-familial Angiomatosis," *Jadassohn's Handbuch*, 12:375-468, 1932 (430-432 and References 463-464); Springer, Berlin.
- WETZEL, NORMAN C.: "Multiple Telangiectasia," *Arch.Dermat.& Syph.*, 25:1162-1164, 1932.
- WIBAUT, F.: *Nederl.tijdschr.v.geneesk.*, 3:4226, 1931. (Menformon in Retinitis Pigmentosa.)
- WILLEBRAND, E. A., AND JÜRGENS, R.: "Die Konstitutionelle Thrombopathie," *Klin. Wchnschr.*, 12:414-417, 1933.
- WISE, FRED: "Hered. Essential Telangiectasia," *Arch.Dermat.& Syph.*, 25:973-974, 1932; *Zentralbl.f.Haut-u.Geschlechtskr.*, 42:733, 1932.
- WITTKOWER: *Zentralbl.f.Haut-u.Geschlechtskr.*, 43:724, 1933; *Dermat. Ztschr.*, 66:181, 1933.
- WITTS, L. J.: "Hereditary Haemorrhagic Diathesis," *Guy's Hosp.Rep.*, 82:405-474, 1932.
- WORDLEY, E.: "Epistaxis without Telangiectasia," *Lancet*, 123:1331, 1932.

ADDITIONAL REFERENCES OF INTEREST

- AUBERTIN, CH., LÉVY, R., AND MME. BACLESSE: "L'angiomatose hémorragique familiale; maladie de Rendu-Osler," *Presse méd.*, 41:185, Paris, 1933.
- BRAUN, JACOB: Reported two families before the Hungarian American Medical Association, New York City, May 4, 1933.
- GROBER, J. (Jena): In Guleke, Penzoldt and Stintzing's *Handbuch der Gesamten Therapie*, G. Fischer, Jena, June 1920, 1:948, sixth edition; "Hämorrhagische Diathesen"—Behandlung—"Da Frauen gar nicht oder jedenfalls sehr selten an Hämophilie erkranken, gab man den männlichen Bluttern Eierstockspräparate, jedoch ohne Erfolg."
- HADEN, RUSSELL, L.: "Pathologic Hemorrhage," *Ohio State M.J.*, 29:487-492, 1933.
- KUFS, H.: *Ztschr.f.d.ges.Neurol.u.Psychiat.*, 113:651, 1928.
- LEVINE, V.: "Angiomatous Malformations of the Brain," *Arch.Path.*, 15:340-351, 1933.
- NEUMARK, SAMUEL: "Osler'sche Krankheit," *Zentralbl.f.Haut-u.Geschlechtskr.*, 44:144, 1933. (63-yr.-old man, mother and brother.)
- RICHTER, WM.: *Dermat.Ztschr.*, 66:137-141, 1933.

- SAMSON-HIMMELSTJERNA, H.V.: "Gedanken über das Wesen der Hämophilie und ihre ursächliche Behandlung," *München.Med.Wchnschr.*, 73:986-989, 1926; *M.J.& Rec.*, 124:329-332, 1926.
- VON BROICH: *Monatschr.f.Geburtsh.u.Gynäk.*, 71:25-32, 1925.
- STRAUSS, A.: *Ann.Otol.,Rhinol.& Laryngol.*, 42:230-239, 1933.
- PECK, SAMUEL: "Congenital Telangiectasia," *Arch.Dermat.& Syph.*, 27:695, 1933.
- HUTCHINSON, J.: *Arch.Surg.*, 7:71-72, 1896.
- NEMIROVSKY, S., AND AMERISO, J.: *Rev. méd.del Rosario*, 23:312-317, 1933.
- ROSENTHAL, F., AND UNNA, P.: *Klin. Wchnschr.*, 12:865-868, 1933.
- TORRIGIANI: *Arch.ital.di otol.*, 44:28-32, 1933.
- WITTKOWER, E., AND RAREY, B.: *Ztschr.f.klin.Med.*, 124:41-46, 1933.
- SCARFF, GORDON R.: *Bristol (England) Med.-Chir. J.*, 50:113-120, 1933.
- GOLDSTEIN, HYMAN I.: *Presse méd.*, 41:152, 1933. (Abstracted by Dr. R. Burnier.)
- MEIKLE, G. J.: *Lancet*, 225:863-864, 1933.
- READING, B.: *Texas State J.Med.*, 28:462-464, 1932.
- CIRIO, G.: *Riforma med.*, 49:598, 1933.
- AUBERTIN, C., AND SEE, GEORGES: *Sang*, 7:851-855, 1933.
- COCKATNE, E. A.: "Inherited Abnormalities of the Skin and Its Appendages," Oxford University Press, London, Chapter IV, pp. 111-117, 1933.
- ULLMANN, KARL: *Urol.& Cutan.Rev.*, 37:619-628, 1933.
- WILLEBRAND, E. A. v., AND JÜRGENS, R.: *Deutsches Arch.f.klin.Med.*, 175:453, 1933.
- ROSENTHAL, F., AND UNNA, P.: *Dermat.Wchnschr.*, 97:1251, 1933.
- DEBENHAM, R. K.: *Brit.J.Surg.*, 21:44-62, 1933.
- NEUMARK, SAMUEL: *Zentralbl.f.Haut-u. Geschlechtskr.*, 44:144, 1933.
- ROSENTHAL AND UNNA: *Ars Medici* (Vienna), 11:509-510, 1933.
- BREM, J., AND LEOPOLD, J. S.: *J.A.M.A.*, 102:200-202, 1934.
- HYNEK, K.: "Nouvelles Considérations sur l'Hémophilie," *Annales de Méd.* (Paris), 14:124-155, 1923; (Hynek and Prerovsky) *Revue Médicale de l'Est*, April 1926.

Surgery

OPERATIVE SHOCK*

By PROFESSOR E. REHN, M.D.

Professor of Surgery, University of Freiburg, Germany

THE word "shock" was coined to describe a very grave failure of the circulation and of other vegetative functions which occurred after accidental injuries and on the battlefield. The violence of inception, the extreme suddenness of appearance, the close connection with trauma, and the threat to the body's functional integrity,—all found expression in this word.

I deliberately set this old traditional surgical concept of shock at the head of my discussion, because it also underlies a second form of surgical shock, namely, operative shock. Surgical shock is admittedly a circulatory disturbance. Hence it is a clinical responsibility which we often have to share with the internist. His scientific investigations on shock have proved invaluable to us, as have also those of the related scientific branches of medicine. This is gratefully acknowledged.

We meet the expression "shock" in many departments of medical practice and investigation and the most varied conceptions and explanations are offered to account for its occurrence and course. The serologist speaks of anaphylactic shock; the neurologist and the psychiatrist of psychic shock; the experimental physiologist uses peptone and histamine shock as the starting point for his discussion of the subject.

All of these considerations have served to contribute to the conception of shock the idea of a sudden occurrence precipitated in one way or another by some factor acting from without and followed by severe circulatory manifestations of a peripheral and central nature, together with disturbances of other vegetative centers. All in all this is the state of affairs which is also found in surgical shock.

* From the Surgical Clinic of the University of Freiburg, Germany.

However, all of these conceptions represent something which is fundamentally different from surgical shock. The tendency to identify them or merely to compare them, I look upon as the initial error which has led to a second error, namely, an attempt to explain the nature of surgical shock and collapse from inferences drawn from them. These fallacies appear to me to be due to the fact that non-surgical investigators very seldom get an opportunity to study the trauma of operation, the state of anesthesia, or the combined effects of these two upon the surgical patient. Therefore, they must base their considerations only upon experience with other types of circulatory disorders or the results of animal experimentation.

A real distinction seems to exist between the phenomena of so-called injury shock and those of operative shock and this distinction has occasioned confusion even among surgeons. Injury shock tends to begin with an erethistic stage and only later to evolve into a depressive phase, whereas operative shock starts out at once as a picture of depression and continues as it begins.

On this score the following remarks are pertinent. Observations upon pure injury shock are rare, due perhaps to the great difficulty encountered in investigating the condition at an early stage. More important is the fact that an individual organism may respond to trauma in a distinctive way and may respond differently to the same trauma at different times. Since the nervous origin theory of injury shock is at present favored it is reasonable to assume that some special state of the nervous system may explain these varying responses. Besides, there are facts to support this view. From the well-known sluggishness and lowered reaction time of wild animals during the rutting season, we may conclude that the sex-hormone befores not only the psyche but also the sensory and vegetative nervous system. In moments of intense emotional excitement, such as is experienced by soldiers attacking the enemy, injuries of the most severe sort can hardly be felt, to say nothing of evoking shock, providing they are not immediately fatal and do not cripple the individual's movements. I might mention, too, the well-known influence on the nervous system and circulation of climatic factors.

The surgeon, preparatory to operation, carefully influences the psyche and nervous system of the patient. He has learned to supplant the method of suggestion, practised by the surgeon of an

earlier day, with careful physio preparation and the alleviation of pain. It is worth remembering in this connection that the vegetative nervous system becomes less irritable under general anesthesia.

The following clinical and experimental facts upon the subject are well known. According to the investigations of Rein and Rössler, heat regulation is suspended during anesthesia because impulses from the heat receptors of the skin are intercepted and this exercises a decided influence upon the blood pressure regulating apparatus. Again, under anesthesia, the vasomotor system is less sensitive to pharmacological stimuli. This is true also for the heart and the vascular reflexes. These effects of anesthesia upon the circulation are shown further by the fall in blood pressure and the change in circulating blood volume which occurs with certain commonly used anesthetics, for example, chloroform, ether, avertin and spinal anesthesia. Yet, again, under general anesthesia the main factors causing traumatic shock are absent, for psychic irritability and pain perception are obliterated and the vegetative system depressed.

In postoperative shock, just as in traumatic shock, we often find an alert, sometimes an over-alert, sensorium after deep and prolonged narcosis. This manifestation of excitement may not occur. Under these circumstances we are, as a rule, confronted by the very gravest situation which may at any moment prove fatal, the early symptoms of shock passing at once to those of collapse. This fatal collapse is due to secondary changes in the composition of the blood and in the nervous system which replace the circulatory manifestations of shock. A detailed account of these secondary disturbances, which have especially interested us, may be found in numerous publications from this clinic.

If a free interval of normal circulation with good average blood pressure occurs (without recourse to pharmacological procedures) between the operation and a circulatory disturbance coming on more than eight hours later, it should not be spoken of as a beginning shock, but rather as a true postoperative collapse. Still less should the condition be called shock if this disturbance makes its appearance after a period of days. This holds true especially if the cause of the collapse may be identified as organic operative damage and anesthesia damage, or if it has been preceded by some severe preoperative disease, especially of the circulatory organs. One may also speak of col-

lapse when a state of shock has led to organic nutritional disturbances, which bring about, long after, an acute circulatory weakness. It was really this type of illness which Sauerbruch recently referred to at Salzuffeln.

Proceeding from these preliminary remarks about surgical shock and postoperative shock, the following conclusions may be drawn. The view of Thannhauser has much in its favor. He insists that the so-called erethistic phase alone should be regarded as the "state of shock" proper, while he designates as "collapse" all of the symptoms of circulatory failure. This is an effort sharply to define the idea of shock and to separate it from collapse. However, we feel that the term shock should express more than the classical erethistic phase. A trauma may not merely stimulate, but also depress, in proportion to the strength of the trauma and the duration of the stimulus. Crile has shown that in long-sustained traumatic shock, the reflex stimulation of the vasomotor center through pain not only does not excite, as during the early stages, but depresses. Our clinical observations have demonstrated what Fischer earlier emphasized, that fleeting transitions can occur between the erethistic and the depressive phases.

The etiology of the circulatory disturbances must be the measure of our surgical conception of shock because it alone justifies the therapy that still to-day is the most effective—prevention. This etiology is a traumatic one in all severe circulatory disturbances after injury or operation.

Hence, I believe we should remain unconditionally with the old accepted terminology in describing grave failures of the circulation and of the vegetative functions after both injury and operation. In those following injury the violent trauma is so overwhelmingly important that it makes no other explanation possible. And the picture presented at the onset of pure injury shock is never seen in collapse.

I have also regarded it as wholly erroneous to identify operative shock with collapse. The final condition of the circulation may in many cases be the same; the state of shock may end in a fatal collapse; yet the cause—and here is the important point—is fundamentally different. Hence I have drawn parallels between injury shock and operative shock throughout my discussions of the erethistic phase.

I must now finally take up the question whether surgical opera-

tion really produces trauma. Every operation, no matter how inconsiderable, puts a burden on the organism. I will here disregard the psychically potent factors which we have to some extent learned to eliminate. Of the many remaining disturbances which the trauma of operation can cause, those in the nervous system and in the circulation itself are to be considered as the source of operative shock. During operation, sensory stimuli are blocked off from the nervous centers. In a state of general unconsciousness, of partial and of local anesthesia, the vegetative system alone remains responsive, although it, too, undergoes a certain amount of suppression in general anesthesia.

The finely adjusted regulatory mechanism of the circulation is very sensitive to operative trauma. We will mention here only the effects upon it of heating and cooling; of the adjustment of collateral circulation; of the consensual functioning of the vasomotors; of the release reflex through the blood-pressure regulator, and of the blood-vessel reflexes proper.

Another point of great surgical significance is the effect of the vagus reflex on the coronary vessels. Their narrowing through vagal stimulation, demonstrated by Rein, explains at once the clinical observations of Reisinger and myself concerning disturbances of conduction during abdominal and thoracic operations. These disturbances, the cause of which could not be explained at that time, are to-day accepted as due to vagal stimulation.

Regarding the effect of splanchnic stimuli on the peripheral circulation, Reisinger and Schneider, of my clinic, have demonstrated a marked diminution in the amount of circulating blood and true shock following tearing of the mesentery.

Especially impressive are stimuli which act on the midbrain and medulla. These come into play during brain operations, for example, through variations in pressure.

The lungs and pleura are very important receptor fields for reflexes going to the heart and vessels. I refer you to the work of Sauerbruch and his pupils, and to Kaufmann's extraordinarily lucid exposition entitled "Circulation and the Nervous System."

Disturbances of richly vascular areas which interfere with the normal blood distribution, such as occurs in operations upon the abdominal and thoracic cavities, are of the greatest importance as

sources of surgical trauma. For an understanding of these disturbances, I may simply say that the movement to and fro of a certain amount of blood is essential in order that a constant blood pressure be maintained. Every laparotomy infringes upon this mechanism, it causes a diminution in blood pressure and in the amount of blood in circulation. With blood engorgement due to defective circulation; with loss of compensation resulting from vasomotor disturbances; with poor nutrition of the heart and of the nervous centers as well; the picture of profound operative shock is completed.

The part which the blood vessels of the liver, spleen and mesentery play in the abdominal cavity and in laparotomy shock corresponds to that played by the lesser circulation and the large thin-walled veins in the chest cavity. Therefore, changes in the normal pressure relations of the chest cavity can lead to conditions and dangers quite similar to those that are well-known to occur in shock. Although our knowledge is still rudimentary concerning the effect of stimuli on the vegetative system, and endless things are yet to be discovered concerning the distribution of the blood under the influence of operation, the traumatic nature of operation may be considered established. We may also consider it proved that operative trauma begins in those places which are certain to participate fundamentally, directly or indirectly, in every case of shock. I emphatically rule out all operative accidents which lead to morphologically identifiable organic damage which in turn produces circulatory disturbances. I would also exclude postoperative disturbances of an endocrine nature.

In reviewing the direct action of operation on the circulation and in its relation to the occurrence of shock, we must distinguish between different regions of the body. Decisive are the relations of operation to certain large vascular areas and also to the vegetative nervous system, peripherally as well as at its sensitive centers.

We have replaced empiricism with hard won knowledge and we now understand why, based on modifications of our biologic concepts which have developed during the past decades, a wholly different technique had to be evolved for carrying out particular operations, for the surgery of extremities and body surfaces, of abdomen, thorax, brain and spine.

Many clinics have specialized in the particular care of certain

provinces, depending largely upon the influence of a great teacher or of some old master. A strength and a weakness lie therein: a strength in the fulness to which special detailed operations are developed, a weakness in the danger of one-sided specialization which neglects other important spheres. The greatest and most difficult goal of a surgeon's life is versatility. He attains this valuable end not only through perfection of technique but also through expansion of his biological knowledge.

The physical condition of the patient has a profound relation to operative trauma and hence to operative shock. This I have sometimes called the operative danger or shock predisposition. We have been especially concerned in my clinic to discover the balance between the burden of operation and the strength of the patient—that is, accurately to diagnose the risk of operation.

We have found a labile state of the circulation to be the essence of operative danger. This is frequently latent and must be recognized indirectly. I have contrasted toxic central liability with such illnesses as primarily cause peripheral disturbance and only secondarily become threatening. The immense importance of this type stands out when I say that we have found them to constitute 24 per cent. of all severe surgical illness.

Von Bergmann calls this operative danger-state "inflammable hypersensitivity." We have busied ourselves generally and specifically with its particularly important forms—in appendicitis, cholecystitis, osteomyelitis, pleural empyema.

If this sensitivity reaches a high level, operation may quickly induce a state of severest circulatory failure, however slight and carefully planned the operation may be. Here the failure of circulation and of other vegetative functions may be termed collapse, because we are far removed from what should be considered the single legitimate cause of surgical shock, namely trauma. This holds especially true if, on top of the pre-existing condition of allergic inflammability (Rossle), the operation facilitates the absorption of decomposed protein, or the release of toxin from the focus of inflammation.

These cases form the transition to the group of vascular disorders which occur through endogenous or exogenous poisoning, that is, the collapse syndrome. The circulatory disturbances caused by histamine and peptone are included in this group.

The symptoms of postoperative shock have frequently been blamed upon histamine, but this view has been conclusively disproved by the numerous observations of my assistant, Herm. Schneider. The symptoms which Cannon and Beylis took to be due to the toxic effect of resorbed substances, Blallock and Smitt have shown to be circulatory disturbances caused by the loss of a large amount of blood in the crushed muscles. Scientific investigation must have the last and most important word about the fundamental nature of postoperative circulatory disturbances and hence concerning the onset and course of operative shock. Such investigation should be made before and immediately after the operation, and in connection with a great number of operations of all kinds.

We investigate the peripheral circulation and the heart. Methods are useless which reveal the momentary state of the circulation and not its functional capacity. The most commonly used method of investigating the peripheral circulation is to estimate the blood-pressure, but this is of little value, as Tigerstedt and many contemporary physiologists and internists have shown. Nor do we get reliable information about the functional capacity of the circulation from a comparison of pulse rate and pulse pressure. Indeed, these observations often lead to erroneous conclusions. Similarly, electrocardiographic investigation of the heart can give information solely about disturbances of rhythm and the condition of the heart muscle, but not about the functional capacity of the heart.

Only those investigations are reliable which quantitatively gauge the dynamics of the circulation. To this end, we determine by known means (Haldane, Van Slyke, Broemser) the amount of blood circulating peripherally and the work of the heart centrally, expressed in minute volumes. The results of these observations stand first in our estimate of the state of the circulation, and only in relation to these do the pulse rate and blood pressure acquire any significance. Such a procedure is altogether reliable in skilled hands, and is absolutely harmless even to the very ill.

In evaluating the results, the state of unconsciousness, the severity of the operation and the type of illness are to be borne in mind.

The following generalizations may be made concerning the nu-

merous circulatory disorders which have developed under our observation.

1. If we compare the effects of operation with a load of work put upon the body, the sound person with a normal circulation must react with an increased minute volume output if the blood volume remains constant or is a little increased. Observation shows that this response does really occur.

2. Diminution of the volume of the circulating blood alone means a postoperative disturbance of the circulation towards the side of depression. Increase of minute volume is the expression of successful compensation. But even at that we stand at the threshold of shock.

3. Shock can occur if the amount of circulating blood diminishes further so that the supply to the heart becomes so scanty that in spite of an increase of rate it cannot maintain the circulation in equilibrium, and the heart itself suffers from an inadequate supply of blood.

A damaged heart cannot meet the increased demand put upon it when the circulating blood volume is diminished and a lowering of the minute-volume output occurs. This is a sure sign, in combination with other clinical manifestations, of approaching shock.

Although death from pure operative shock is rare to-day as compared with former times, still, postoperative disturbances of the circulation are of great significance for the surgeons of to-day, since the secondary changes in blood distribution and in the central nervous system frequently terminate in fatal collapse. Indirect results of these alterations may be observed later as thrombosis, embolism, pneumonia and delayed collapse. These come from changes inaugurated by shock in the circulation itself and in specially sensitive organs.

What has been said about predisposition to shock, shock-sensitive portions of the body and operative technique flows naturally from the biological laws which have been exposed. Therefore, it follows that the consideration of postoperative circulatory disturbances is something more than a purely scientific question and their significance more than what was contained in the original conception of shock.

THE ANTERIOR LOBE OF THE PITUITARY GLAND, THE THYROID GLAND AND THE CARBOHYDRATE METABOLISM OF THE LIVER*

By HERMAN EITEL, M.D.

Assistant in the Clinic

and ARNOLD LOESER, M.D.

Assistant in the Institute, University of Freiburg, Germany

I. INTRODUCTION

PHYSIOLOGY, pharmacology and clinical medicine are equally occupied with the problem of the function of the anterior lobe of the hypophysis. Since the fundamental work of Evans¹ and his school, as well as that of Ascheim and Zondek,² this domain of the internal secretions has become an ever extending field for investigation. However, knowledge has not kept pace with the vast number of experiments, so that at present we are unable to draw, from the observed facts, conclusions which are entirely satisfactory and generally applicable.

The extensive investigations of the last few years upon the relation that exists between the hypophysis and the thyroid gland (Aron,³ Loeb,⁴ Verzàr,⁵ Janssen and Loeser,⁶ Loeser⁷) have shown definitely that the symptoms which follow the injection of hypophyseal anterior lobe substance are very similar to those which are characteristic of hyperthyroidism. The elevation of the basal metabolism, the exophthalmus, the reduction of the amount of iodine in the gland and the concomitant increase of the iodine in the blood and lastly the histological picture of a greatly altered thyroid gland—irregularly formed acini, enlargement and proliferation of the acinar epithelium, liquefaction and disappearance of colloid—justify the assumption that these changes are produced by a thyroid gland stimulated to overactivity by the injection of anterior lobe substance. It may be objected to this interpretation that up to now no one has succeeded

* From the Pharmacological Institute and the Surgical Clinic of the University of Freiburg, i.B.

in actually demonstrating the presence of still other well known manifestations of thyroid secretion.

However, although we cannot directly demonstrate thyroid gland hormone in the blood, still certain evidence makes probable its presence there. In Basedow's disease, as well as in experimental hyperthyroidism following the injection of anterior lobe substance, the blood will produce some of the effects which are characteristic of thyroid gland activity. The increased iodine content of the blood is further evidence favoring the assumption that thyroid substance is actually in the blood (Salomon,⁸ Schittenhelm and Eisler,⁹ Schittenhelm,¹⁰ Grab,¹¹ Schneider and Widmann,¹² Loeb, Closs and MacKay¹³).

If we interpret the above cited observations to indicate an increased thyroid activity, then we would expect to find, in addition to the manifestations described, still other evidence of functional alteration of the gland.

Naturally, those organs which are particularly concerned with removing the toxic elements of the thyroid hormone would be the first to show these effects. Abelin¹⁴ has demonstrated that the liver is chiefly concerned in this action. However, only a healthy liver can exercise the function. Evidence that the liver is affected by the thyroid hormone is furnished by the well known glycogen, fat, creatin and creatinin depletion of the organ (Albelin).¹⁵ The ability to store glycogen and fat is lost. The more seriously impaired this function of the liver may be the more intense are the manifestations of the hyperthyroid state. From the standpoint of treatment it is important to maintain a normal liver function in order to diminish the effects of hyperthyroidism.

Assuming that the injection of anterior lobe substance produces effects analogous to those of hyperthyroidism, it becomes necessary to furnish evidence to prove:

1. That an injection of anterior lobe substance will decrease the glycogen content of the liver just as thyroxin and thyroid gland substance.
2. That the glycogen reduction is brought about by the action of the thyroid gland.

Concerning this relation there are a number of contradictory observations. Fukui¹⁶ found no change in the total carbohydrate

content of the liver after injecting "Pituglandol", "Hypophysin", "Pituitrin" or an anterior lobe preparation called "Sanabo", whereas Houssay and Biasotti¹⁷ found in normal toads that the glycogen reserve of liver and muscle was increased by the injection of anterior lobe substance but was diminished when the pancreas had previously been removed.

II. METHOD

Young guinea pigs were used as experimental animals. They were kept at an even room temperature, four to a cage including controls. They were fed turnips and hay. They were given enough food so that at each daily feeding some food from the day before was left over. Their weight and temperature was regularly recorded. Preparation of the anterior lobe was injected intraperitoneally. Before doing the glycogen determinations,¹⁸ we allowed the animals to starve for eight hours, after which they were given 0.75 Gm. of levulose per 100 Gm. of body weight in a 50 per cent. solution. The animals were then killed by a blow on the neck six hours after the administration of the carbohydrate. The liver was immediately removed, freed from the gall bladder and the bile ducts, quickly cut up and placed in a weighed tube filled with 8-12 Gm. of a hot 60 per cent. solution of potassium hydroxide, a small piece being reserved for histological examination. After again weighing the tube and contents, it was frequently stirred while being heated for three hours in boiling water, then cooled, the contents diluted with water, transferred to a beaker, and the glycogen precipitated with 96 per cent. alcohol. After standing for several hours the precipitate was filtered off from the supernatant liquid. It was then washed and centrifuged several times with 60 per cent., 96 per cent., and 100 per cent. alcohol. The glycogen thus obtained was then hydrolyzed with hydrochloric acid and the amount of sugar determined by the Bertrand method. From this determination the glycogen content of the liver is calculated. The blood sugar was estimated by the Hagedorn-Jensen method.

III. GLYCOGEN CONTENT OF THE GUINEA PIG LIVER

The first important step was to determine the glycogen content of the liver in a large number of guinea pigs so as to have a standard

TABLE 1
Control Animals

Animal No.	Body Weight in gr.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
168	165	91,6	2,3	18,2	0,6	74
581	225	90,9	2,1			
586	170	72,1	2,6			
587	175	31,9	2,1			
126	190	142,6	2,7			68
140	265	136,1	1,9	17,8	0,5	102
127	305	135,3	1,6			88
111	190	130,7	2,5			
101	200	118,7	3,1			97
106	185	114,8	3,6			
102	210	127,9	2,8			120
588	165	40,3	1,3			
588	190	216,3	4,1	16,7	0,49	70
590	215	75,4	2,9			
589	155	133,3	3,9			93
593	225	121,4	2,5			
592	215	153,4	3,5			98
595	156	90,8	2,6			
596	155	67,2	1,8			
609	175	76,8	2,1			
610	175	86,5	2,5			

Averages: 2,59

0,52

with which to compare subsequent observations. Table I illustrates the results. The estimates obtained from twenty-one animals show in spite of constant conditions, wide individual variations. On the average the guinea pig liver contains 2.59 per cent. glycogen. The muscle glycogen was less variable, 0.52 per cent. being the average. The blood sugar determinations in the same animals varied from 68 and 120 mg. per cent. To control the chemical results the liver was also examined histologically, as it was in all later experiments, and the glycogen stained red by the Best method. The illustration (Fig. 1) shows such a microphotograph with the characteristic central arrangement of the glycogen particles in the liver lobules.

IV. THE EFFECT OF THE THYROTROPIC SUBSTANCE OF THE ANTERIOR LOBE ON THE THYROID GLAND AND THE GLYCOGEN CONTENT OF THE LIVER

To investigate the relation between the anterior lobe of the hypophysis and carbohydrate metabolism it seemed particularly worth while to discover whether the glycogen content of the liver varies with morphological changes in the thyroid gland. But before we go to this question we wish to bring up another which has only recently been satisfactorily answered, namely, is the effect of the anterior lobe of the hypophysis a specific one and is there a connection between the effect on the thyroid and on the sex organs? The experiments of Janssen and Loeser,¹⁹ as well as those of Aron,²⁰ have settled this question since they show that none of the many substances which they tested produce changes in the thyroid gland analogous to those which follow the injection of anterior lobe substance. Furthermore, they demonstrated that the epithelial proliferation and the extensive disappearance of colloid from the thyroid still takes place when a potent hypophyseal preparation (acetone dried powder) is injected into young guinea pigs fourteen days after bilateral oophorectomy. They properly conclude from this result that the effect of the anterior lobe on the thyroid gland is a direct one and does not at all depend upon the presence of the ovaries. However, the question still remains, is this active anterior lobe hormone the same that influences the development of the genital organs? The recent experiments of Loeser²¹ and others²² indicate that it is not and justify the assumption that there is a specific thyrotropic substance in the hypophysis. They succeeded in isolating from the hypophysis a substance which changed the thyroid gland into the hypertrophic condition described. This substance was obtained by treating dried anterior lobe with a solution of ammonium hydrate, freeing the solution of protein with trichloroacetic acid and treating the filtrate with acetone. On the other hand, the residue left after thorough extraction retained the power to affect the sexual organs but had no effect whatsoever upon the thyroid gland. This specific thyrotropic substance was used as a control in our experiments, the preparation used in the investigations having been kindly placed at our disposal by the Schering-Kahlbaum Co. of Berlin (Thyreotropes Hormon des Hypophysenvorderlappens).

We attempted to decide whether the glycogen content of the liver decreases at the same time as the thyroid gland changes in the following way: Groups of four or more animals received daily an intraperitoneal injection of the hypophyseal preparation. A single dose consisted in all cases of 2.5 mg. The autopsy on each group of animals used in the experiment was done on the second, third, fourth, sixth, eighth and twelfth day. The total amount of the substance injected was in the first group 2.5 mg., in the second 5 mg., in the third 7.5 mg., in the fourth 12.5 mg., in the fifth 17.5 mg., and finally in the sixth injection on the twelfth day, 27.5 mg. The animals were killed regularly on the day following the last injection, after the preliminary preparation already described. The result of the first experiment is shown in Table 2. On the average the liver

TABLE 2
Experimental Group 1

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg.%
130	215	215	2,5	2,5	218,3	3,3	31,6	1,2	88
141	220	225	2,5	2,5	215,1	2,7	43,2	1,0	70
138	220	220	2,5	2,5	215,1	3,1			70
166	225	220	2,5	2,5	106,1	1,6			70

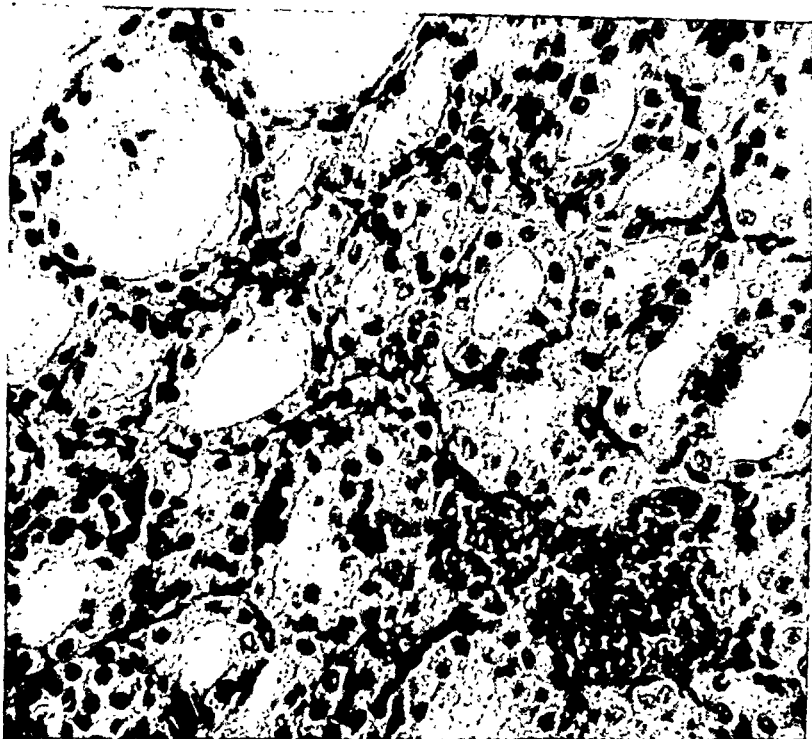
Averages: 2,67

1,1

glycogen content was 2.67 per cent, which is somewhat higher than in the normal animal. Likewise the muscle glycogen was increased to 1.1 per cent.

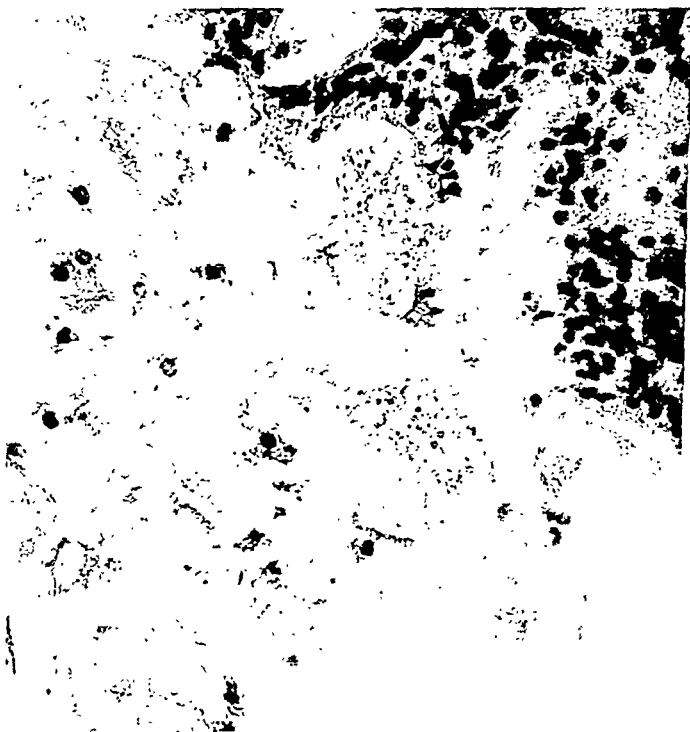
What is the condition of the thyroid gland in the animal treated with anterior lobe extract? The changes within the gland are shown in Fig. 3. In contrast to the normal thyroid of the guinea pig, which is shown in Fig. 2, the epithelium is definitely higher. The form of individual acini is not conspicuously altered. However, the colloid in the central parts of the gland has partly disappeared, is partly filled with small, bright vesicles which indicates beginning

FIG. 3



Thyroid gland of a guinea pig injected with 2.5 mg. of thyrotropic substance of the anterior lobe of the hypophysis. Distinct proliferation of the epithelium, beginning liquefaction of the colloid in the peripherally located acini. Extensive colloid disappearance in the center of the gland.

FIG. 4



Impressive epithelial
of the lumen of the a
pearance of the colloid

TABLE 4
Experimental Group 3

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
580	175	170	2,5	7,5	95,3	2,6	—	—	—
161	250	235	2,5	7,5	103,2	2,0	15,2	0,5	83
146	225	200	2,5	7,5	58,4	1,3	11,5	0,5	79
172	245	225	2,5	7,5	181,9	3,5	—	—	127
181	150	140	2,5	7,5	6,5	0,3	—	—	104

Averages: 1,94

0,5

TABLE 5
Experimental Group 4

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
496	142	145	2,5	12,5	not determinable	not determinable	7,0	0,4	155
491	130	125	2,5	12,5	not determinable	not determinable			
497	115	115	2,5	12,5	not determinable	not determinable			
176	200	195	2,5	12,5	65,4	1,4	—	—	124
490	110	110	2,5	12,5	not determinable	not determinable	5,5	0,3	142
128	200	195	2,5	12,5	5,8	0,1			
144	200	200	2,5	12,5	1,8	0,04			
171	225	220	2,5	12,5	73,6	1,5	—	—	106

Averages: 0,38

0,4

TABLE 6
Experimental Group 5

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
493	195	165	2,5	17,5	1,1	0,02	4,6	0,4	78
177	150	150	2,5	17,5	3,3	0,07	8,9	0,4	—
967	175	160	2,5	17,5	26,9	0,98	—	—	—
975	185	165	2,5	17,5	12,5	0,5	—	—	—

Averages: 0,39

0,4

TABLE 7
Experimental Group 6

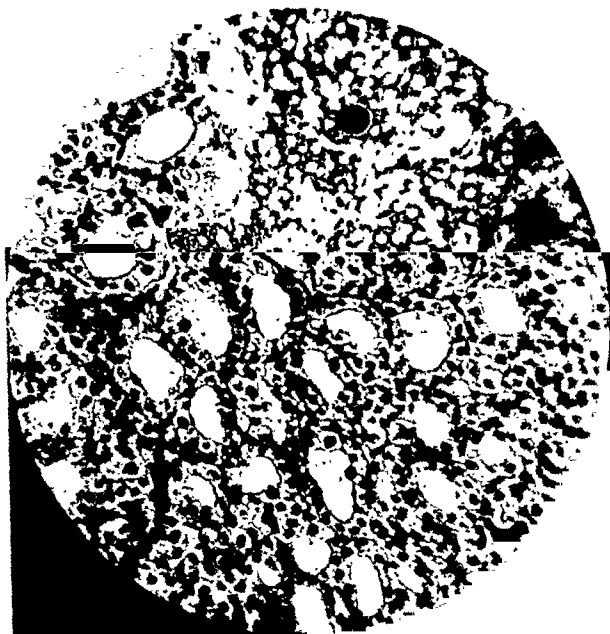
Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
404	213	230	2,5	27,5	not determinable	—	—	—	—
406	200	170	2,5	27,5	not determinable	—	—	—	—
407	140	145	2,5	27,5	not determinable	—	—	—	—
402	190	210	2,5	27,5	9,5	0,24	—	—	—
191	225	195	2,5	27,5	3,3	0,07	10,4	0,4	117
139	220	180	2,5	27,5	10,8	0,2	8,5	0,4	106

Averages: 0,085

0,4

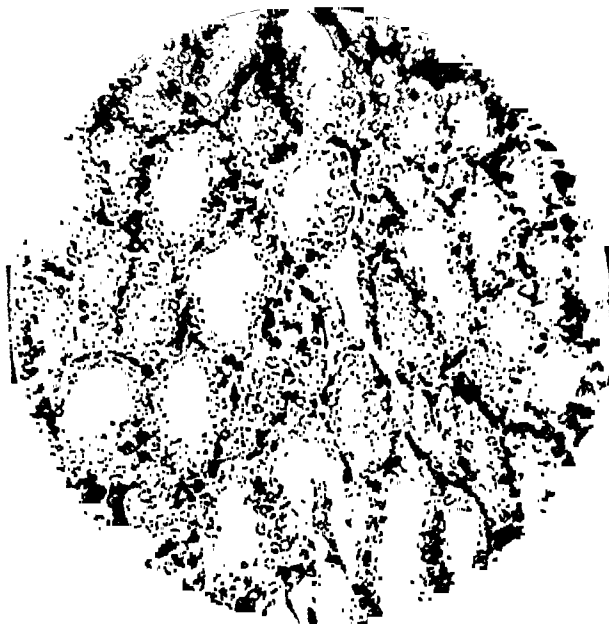
only the average glycogen content, one finds a glycogen decrease of about 70 per cent. In the three day experiment the average amount of liver glycogen was found to be 1.94 per cent., the muscle glycogen 0.5 per cent. The figures corresponding to the five, seven, and

FIG. 5



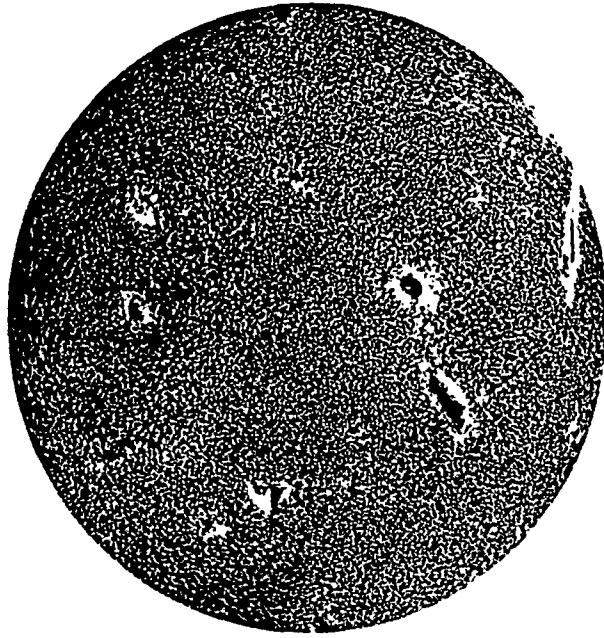
A thyroid gland after the injection of 7.5 mg. of anterior lobe of the hypophysis. Complete disappearance of the colloid.

FIG. 6



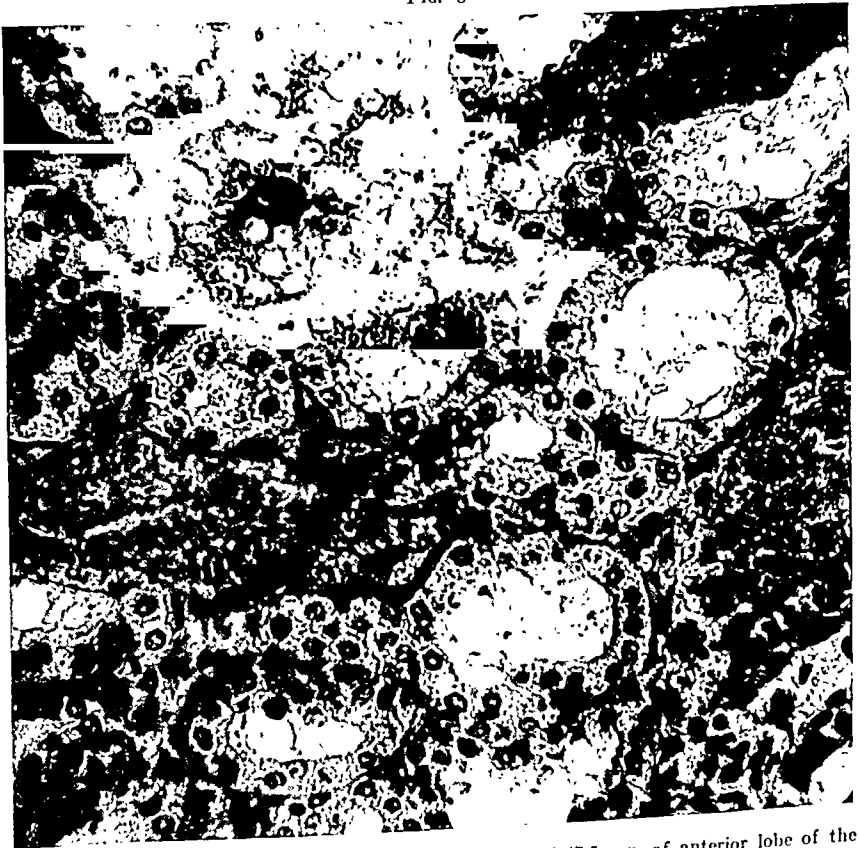
The thyroid gland of a guinea pig after the injection of 12.5 mg. of the anterior lobe of the hypophysis. Maximum formation of epithelial proliferation and disappearance of the colloid.

FIG. 7



Liver after injection of 12.5 mg. of anterior lobe stained by the Best method. The rich heaping of the glycogen in the neighborhood of the central vein is no longer seen.

FIG. 8



The thyroid gland of a guinea pig after the injection of 17.5 mg. of anterior lobe of the hypophysis. Extensively proliferated epithelium, liquefaction of the colloid.

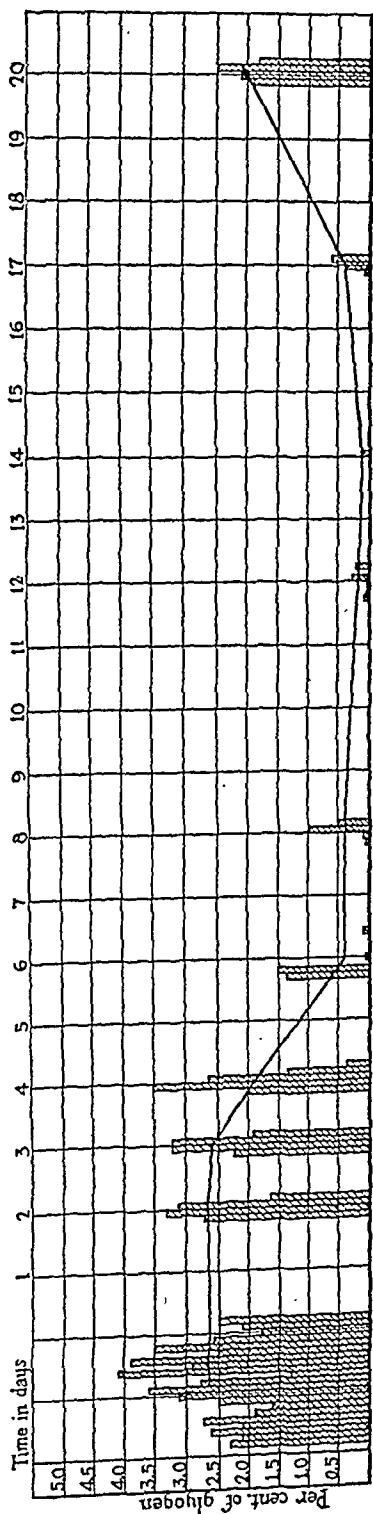
eleven day experiments are 0.38 per cent., 0.39 per cent., and 0.085 per cent. for liver glycogen, and 0.4 per cent., 0.4 per cent., and 0.4 per cent. for muscle glycogen.

Special attention is directed to the differences in the glycogen values in the individual animals of each experimental group. We have already pointed out the wide variations in the groups treated only once or twice. A comparison of Tables 4 and 5 with Tables 6 and 7 will show at a glance that with an increase in the length of treatment there is a progressive tendency for these wide individual fluctuations to disappear and for the amount of glycogen to become more nearly uniform.

The histological changes occurring in these experimental groups may be seen in Figs. 5, 6, 8 and 9. The changes in the thyroid gland have reached the highest degree. The disappearance of colloid is complete. The microphotographs of the liver are excellent companion pieces to the analytical results, since they illustrate conclusively the gradual disappearance of glycogen, clearly demonstrated by the Best carmine stain.

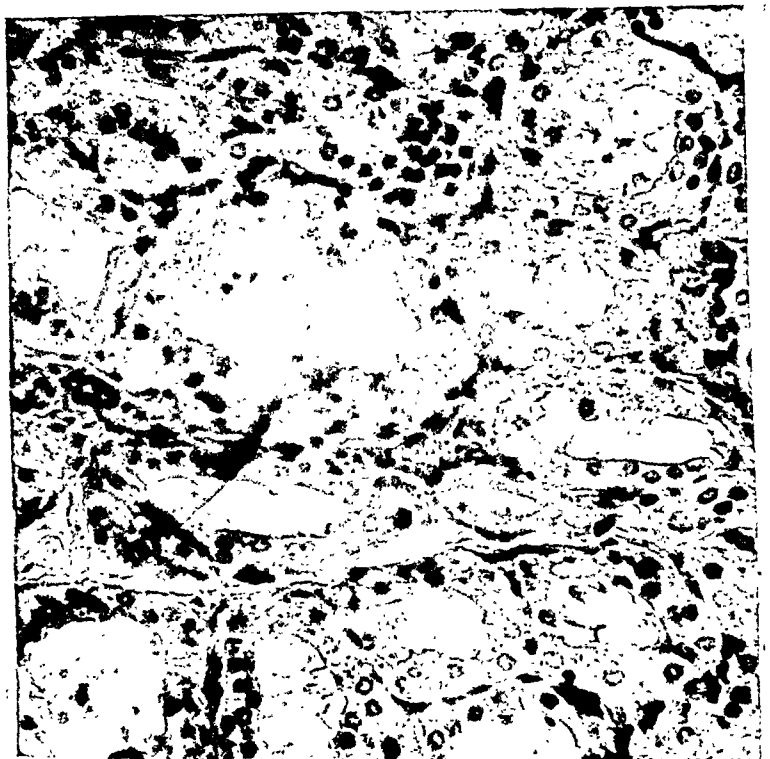
The results and the significance of the experiments so far reported may be summarized as follows: The injection of the thyrotropic substance of the anterior lobe produces changes in the thyroid gland of the guinea pig which are comparable to those found in exophthalmic goiter (*Morbus Basedow*). These changes in the thyroid gland are the expression of increased activity which leads to a depletion of colloid. The glycogen content of the liver is at first unaffected. The first two injections cause no appreciable diminution of glycogen. Only after five days of treatment does the glycogen content begin to fall and after seven and eleven injections it reaches a very low value (curve 1). If one injects animals, previously given levulose, with the usual amount (2.5 mg.), of anterior lobe preparation two hours before they are killed and then determine the glycogen content of the liver, a decrease of about 29 per cent. is regularly observed. This initial loss of glycogen which is accompanied by an increase of acetone bodies in the blood, as demonstrated by Anselmino and Hoffman²³ in the rat, is restored at the end of twenty-four hours. Indeed, the average value found at this time is a little above the normal. The original decrease of the liver glycogen can not be satisfactorily explained, except by assuming an increased

CURVE 1



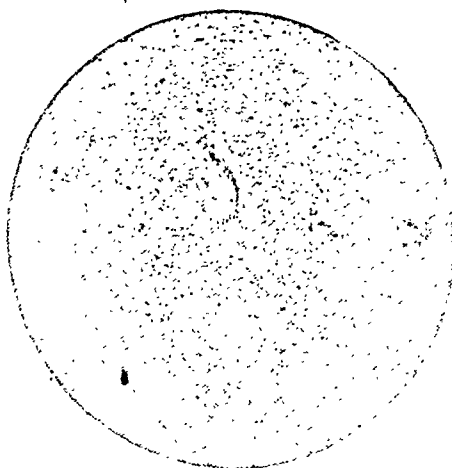
The effect of the repeated injection of the thyrotropic substance of the anterior lobe of the hypophysis on the glycogen content of the liver and its dependence on the duration of the treatment.
 Liver glycogen content per animal in percent.
 The line connects the average value of the liver glycogen for the different experimental groups.

FIG. 9



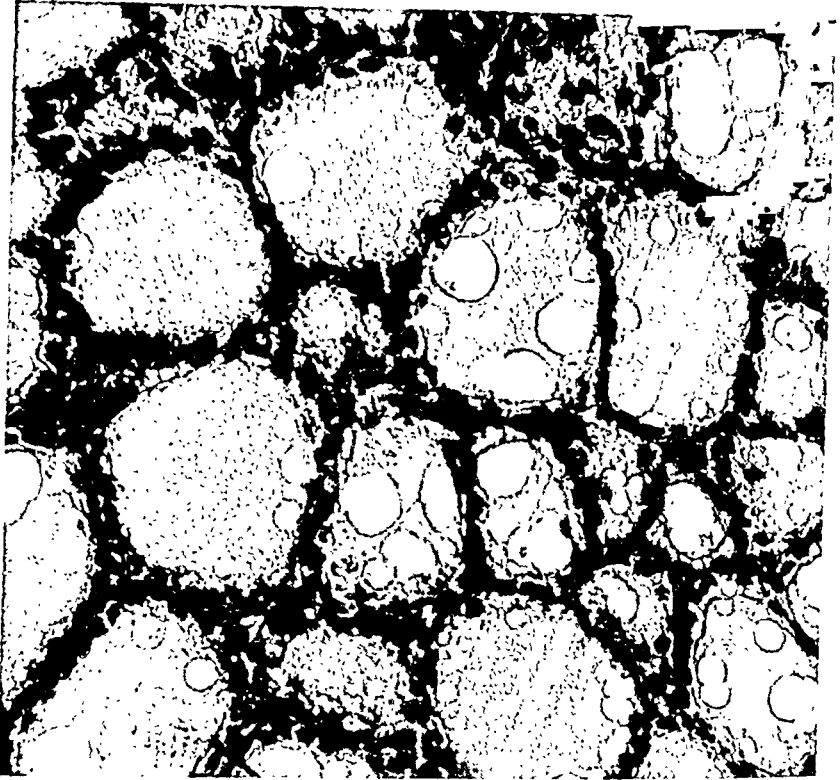
The thyroid gland of a guinea pig after the injection of 27.5 mg. of anterior lobe of the hypophysis. Papillary formation and stratification of the epithelium. No colloid remains.

FIG. 10



Liver after the injection of 27.5 mg. of anterior lobe of the hypophysis. The lack of glycogen in the liver corresponds with the analytical determinations (Animal No. 406).

FIG. 11



Thyroid gland of a guinea pig two hours after one injection of 2.5 mg. of anterior lobe substance. The appearance of vacuoles about the borders of the acini indicates beginning liquefaction of the colloid.

FIG. 12A

FIG. 12B



Electrocardiogram of a normal animal.

Electrocardiogram of an animal treated for twenty days. The animal showed well marked exophthalmus.

activity of the thyroid gland, which, as shown in the histological picture of the thyroid gland, is associated with distinct evidence of the liquefaction of the colloid (Fig. 11). We believe that the over-functioning thyroid gland imposes a burden upon the liver which lasts until a balance is re-established between the two organs.

The diminution of carbohydrates in the liver which follows the ingestion of thyroxin or thyroid extract is most pronounced on the first day after the feeding of these substances.²⁴ Whether the results of our experiments may be compared with these findings we cannot at this time decide.

We have not as yet mentioned the general condition of the animals treated for longer periods. An increased appetite was shown by nearly all of the experimental animals after the injection of hypophyseal anterior lobe substance. Symptoms of excitability were certainly not marked. The body weight showed, aside from occasional fluctuations, no important change. Fever and diarrhoea were not observed. At autopsy no gross abnormalities were noted except the enlargement of the thyroid and of the adrenals. The histological study of the other glands of internal secretion is not yet completed. Many of the animals showed a decided exophthalmus. Similar observations were made by Schockaert²⁵ on ducks. This symptom is not an unusual one in animals. The literature²⁶ contains many instances of true Basedow's disease in animals (race horse, dog, cow, and lion), in which exophthalmus was a constant symptom. The electrocardiogram of a number of our experimental animals shows striking changes which we wish to put on record but hesitate to interpret (Plate 12a and b).

We may now return to the striking fluctuations of the glycogen content of the liver found in the first experiments (experimental group Nos. 3 and 4). A comparison of the weights of various thyroid glands which were carefully removed and dried with the glycogen content of the liver give a surprising result, namely, a high glycogen content was found in the animals with low thyroid weight, whereas low liver glycogen accompanied an increase in the weight of the thyroid. This relation was practically always found—Table 8. The weight differences of the glands in animals of about the same weight seem to us to bear a direct relation to the amount of hormone produced and this appears to be particularly true when the thyroid

TABLE 8

Animal No.	Body Weight in gr.	Weight of Thyroid Gland in mg. (without water)	Thyroid to Body Weight in %	Liver Glycogen in %	Total Amount Injected in mg.
130	215	24	9	3,3	2,5
141	225	16	14	3,7	2,5
138	220	22	10	3,1	2,5
166	220	31	7	1,6	2,5
161	235	24	9,8	2,0	7,5
146	200	26	7,7	1,3	7,5
172	225	19	11,8	3,5	7,5
181	140	21	6,6	0,3	7,5
176	195	35	5,5	1,4	12,5
128	195	26	7,5	0,1	12,5
144	200	38	5,2	0,04	12,5
171	220	18	12,2	1,8	12,5

is stimulated by the thyrotropic substance of the anterior lobe. The larger gland gives off more secretion in the same time than the smaller. This is well shown in the curves illustrating the early period of this effect. We find the greatest fluctuation in values when glycogen first begins to disappear, they become less marked with the duration of treatment, and finally on the eleventh day, they practically disappear.

V. THE DURATION ON THE EFFECT ON THE THYROID GLAND AND THE CHANGES IN THE LIVER AFTER THE INJECTION OF THE THYROTROPIC SUBSTANCE OF THE ANTERIOR LOBE OF THE HYPOPHYSIS

In Curve 1, one may easily see that the glycogen depletion of the liver has reached its highest point on the twelfth day. At the end of the eleventh day of treatment there was an average of 0.08 per cent. However, it still remains unknown how these changes progress after they are once well established and, what is perhaps more important, what happens to the organs after the treatment is stopped. Experiments undertaken to elucidate these questions were carried out as follows: Two animals received daily for thirteen consecutive days 2.5 mg. of the pituitary preparation. The average glycogen content of the liver on the fourteenth day was only 0.05 per cent.

The muscle glycogen was not diminished (0.4 per cent.). However, these findings quickly change when the injections are stopped. The result of one such experiment is shown in Table 9. The liver

TABLE 9
Experimental Group 7

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
878	192	175	2,5	32,5	33,7	0,6	—	—	—
961	215	215	2,5	32,5	18,4	0,4	12,5	0,6	70
951	175	170	2,5	32,5	5,4	0,1	—	—	60

Averages: 0,36

0,6

glycogen content of these animals, which had received injections on thirteen consecutive days, but were killed four days after the injection, is decidedly higher. The average liver glycogen was 0.36 per cent., the muscle glycogen remained unchanged, 0.6 per cent. This result is still more striking if seven days are allowed to pass after the last injection before the animal is killed. The result of this

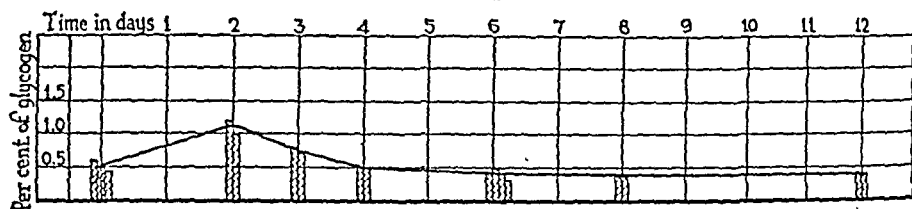
TABLE 10
Experimental Group 8

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Daily Injection in mg.	Total Injection in mg.	Liver Glycogen in mg.	Liver Glycogen in %
410	165	170	2,5	32,5	64,6	1,8
408	180	185	2,5	32,5	93,8	1,9
411	175	180	2,5	32,5	121,6	2,5
125	210	205	2,5	32,5	97,3	2,1

Average: 2,07

experiment shown in Table 10 demonstrates a decided increase of liver glycogen. The explanation of this strange occurrence is given in the histological picture of the thyroid gland (Figs. 13 and 14). The retrogression of the hyperplastic change is obvious. The most noteworthy feature is the gradual reappearance of colloid in the acini previously depleted and the simultaneous increase of glycogen in the liver. The epithelium is distinctly lower. This is indubitable evidence of an increasing secretion of the thyroid gland and its direct dependence upon the duration of the injections of the thyrotropic substance of the anterior lobe. At the moment when this substance is withheld, the secretion of the gland begins to slacken.

CURVE 2



The effect of the repeated injection of thyrotropic substance of the anterior lobe of the hypophysis on the glycogen content of the muscle.

Muscle glycogen content per animal in percent.

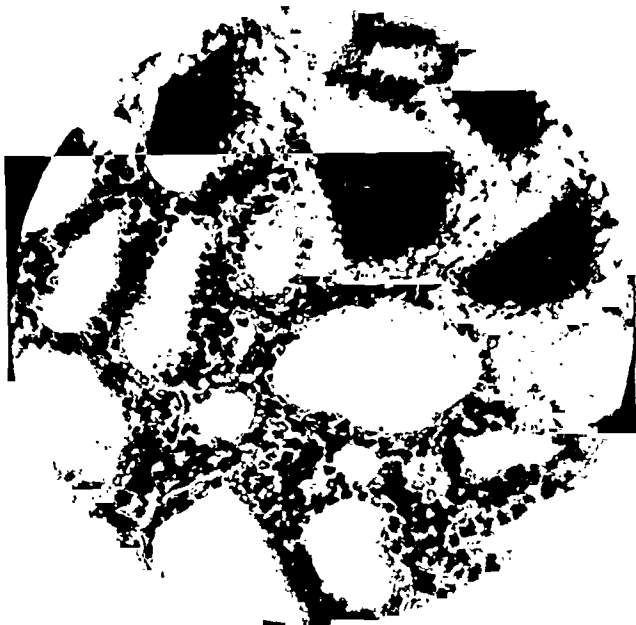
The line connects the average value of the liver glycogen of the different experimental groups.

Then the tax put upon the liver by the increased thyroid secretion is removed and the glycogen content of the liver rises. As the liver glycogen returns the basal metabolic rate, which rises under the influence of anterior lobe substance, begins to fall. The increase in metabolic rate continues, according to the experiments of Verzar and Wahl²⁷, only so long as the supply of the hypophyseal substance is administered, and returns to normal from four to six days after the injections are stopped.

VI. THE EFFECT OF THE THYROTROPIC SUBSTANCE OF THE ANTERIOR LOBE OF THE PITUITARY ON THYROIDECTOMIZED ANIMALS

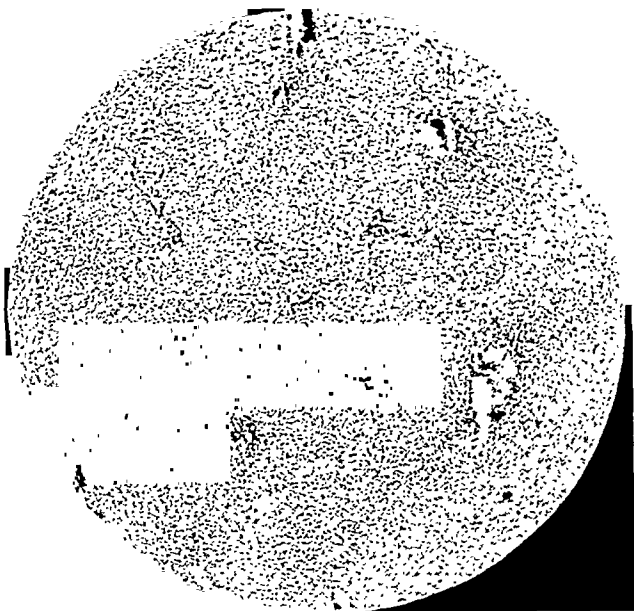
The great activity of the thyrotropic substance of the anterior lobe and the identity of its effects with those of whole thyroid gland have led us to look upon the other observed changes as released by the thyroid. This conception however requires further experimental proof. The proof will be furnished if we can demonstrate that the glycogen depletion of the liver, which we have observed, does not occur when the thyroid gland has been removed. This fact we have

FIG. 13



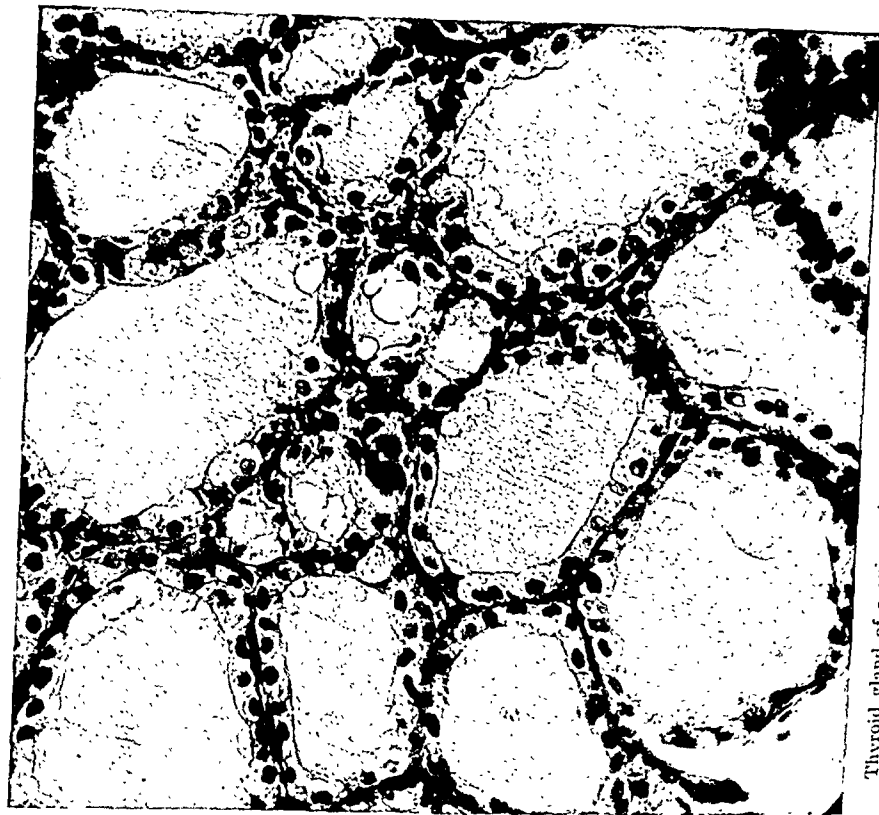
Thyroid gland of a guinea pig after the injection of 32.5 mg. of anterior lobe substance of the hypophysis. The animal was killed four days after the termination of the injections. Beginning depression of the epithelium and enlargement of the acini with spots of lightly stained colloid.

FIG. 14



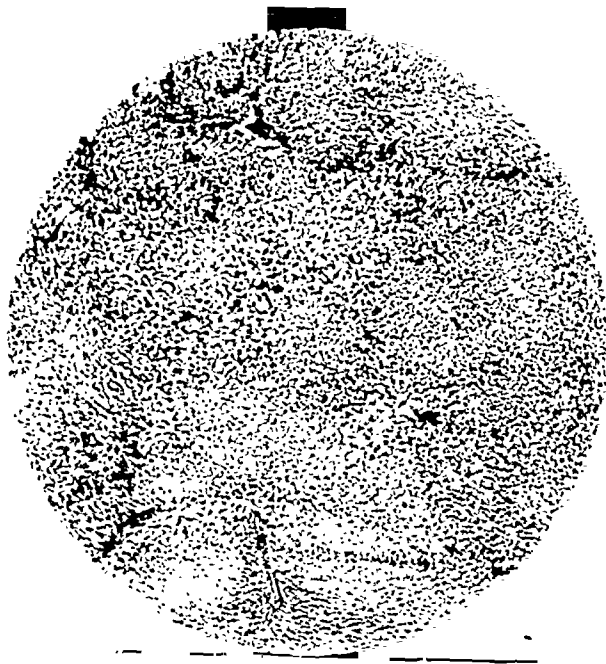
Liver after the injection of 32.5 mg. of anterior lobe substance. The animal was killed four days after the injections were completed.

Fig. 15



Thyroid gland of a guinea pig after injection of 32.5 mg. of anterior lobe substance. The animal was killed seven days after the last injection. Decrease of the cell hypertrophy and cell hyperplasia, and the reappearance of the colloid.

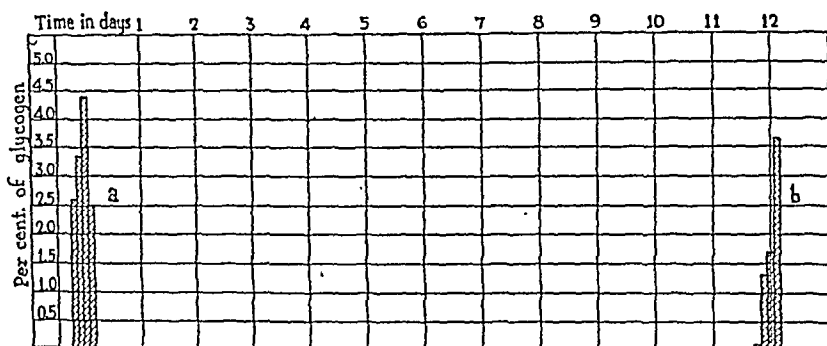
Fig. 16



Liver after the injection of 32.5 mg. of anterior lobe substance. The animal was killed seven days after the last injection. Reappearance of glycogen and in contrast to Plate 1, its accumulation at the periphery of the lobes.

actually demonstrated. We removed the thyroid gland from four animals under urethane anesthesia and determined ten days thereafter the liver and muscle glycogen. Four other guinea pigs, prepared in the same way, received daily 2.5 mg. of the hypophyseal preparation. The total dose was 27.5 mg. On the day after the last injection (12th day), at a time therefore, when the glycogen depletion of the liver of animals not operated upon is at its height, the experimental animals were killed. A comparison of the glycogen content of the liver after the extirpation of the thyroid is shown in Tables 11 and 12 (Curve 3). It is noteworthy that in two animals

CURVE 3



The curve shows the glycogen content of the liver in thyroidectomized animals: (a) before the injection, (b) after 11 days of injection of thyrotropic substance of the anterior lobe of the hypophysis amounting to 27.5 mg.

Liver glycogen content per animal in percent.

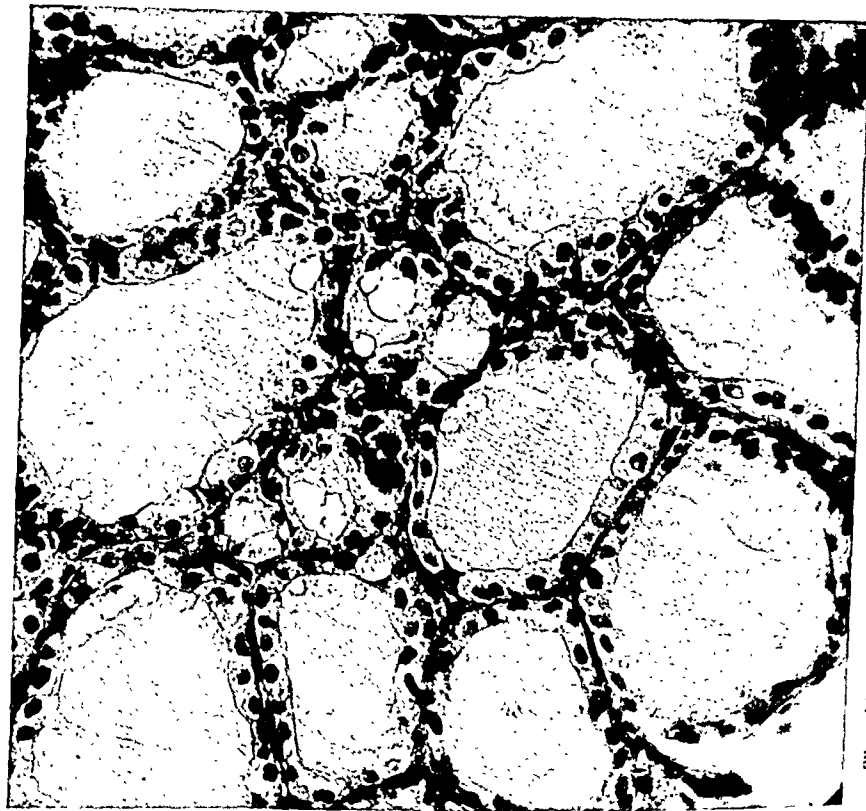
TABLE 11
Experimental Group 9

Animal No.	Weight of Animal before Treatment in gr.	Final Weight in gr.	Liver Glycogen in mg.	Liver Glycogen in %	Muscle Glycogen in mg.	Muscle Glycogen in %	Blood Sugar in mg. %
607	365	405	253,1	2,6	—	—	—
608	320	300	175,7	3,3	—	—	—
610	290	310	464,2	4,4	35,2	0,7	67
152	330	295	292,0	2,5	12,2	0,3	127

Averages: 3,2

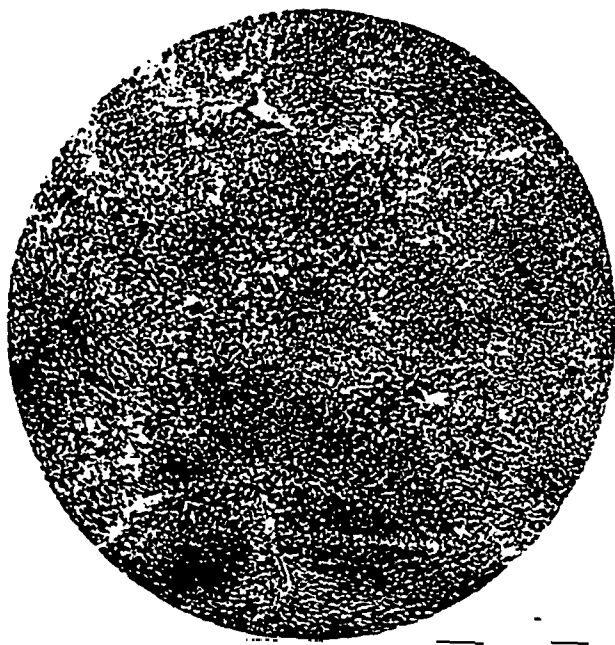
0,5

FIG. 15



Thyroid gland of a guinea pig after injection of 32.5 mg. of anterior lobe substance. The animal was killed seven days after the last injection. Decrease of the cell hypertrophy and cell hyperplasia, and the reappearance of the colloid.

FIG. 16



Liver after the injection of 32.5 mg. of anterior lobe substance. The animal was killed seven days after the last injection. Reappearance of glycogen and in contrast to Plate 1, its accumulation at the periphery of the lobes.

greatly altered masses of thyroid tissue varying in size (Fig. 17). Therefore, the loss of liver glycogen even after thyroidectomy, is clearly explained. This proves conclusively that the glycogen depletion of the liver, which follows injection of the anterior lobe, is a secondary effect due to the hyperfunction of the thyroid gland. These facts agree with the observations of Verzàr and Wahl,²⁸ that the elevation of metabolism which occurs in guinea pigs after the injection of the hypophyseal anterior lobe hormone is less decided when the thyroid has been removed. In a few cases an actual depression of metabolism could be demonstrated. These investigators believe that metabolic depressive effect of the hormone is obscured by the activity of the thyroid in non-thyroidectomized animals.

VII. THE THERMOLABILITY OF THE THYROTROPIC SUBSTANCE OF THE ANTERIOR LOBE

It seems desirable to discuss briefly a question which still is hotly disputed, namely, is the activity of the thyrotropic substance maintained after it has been subjected to higher temperatures? This question is answered in the affirmative by Crew and Wiesner,²⁹ and many others. Thermostability is supposed to distinguish the thyrotropic hormone of the anterior lobe from the hormone which acts upon the sexual organs. Contrary to this, Janssen and Loeser³⁰ failed to note any histological changes in the thyroid gland after injecting powdered anterior lobe which had been boiled for an hour. The iodine content³¹ of the thyroid gland was not diminished. These results make it seem unlikely that the thyrotropic substance of the anterior lobe is thermostabile, as do also those of Loeser,³² who showed that the activity of the thyrotropic substance of the anterior lobe is greatly reduced, depending upon the duration and the degree of heating. The following experiment seems at first to contradict these conclusions. We injected each of four guinea pigs with 5 mg. of thyrotropic substance every day for seven days, the substance having been previously heated in physiological salt solution at 100 degrees for one hour in a reflux condenser. The total dose for each animal was 35 mg. The animals were killed twenty-four hours after the last injection and the glycogen content of the liver determined in the usual way. The results of the experiment were a surprise, since we expected to find no change in the glycogen values, whereas

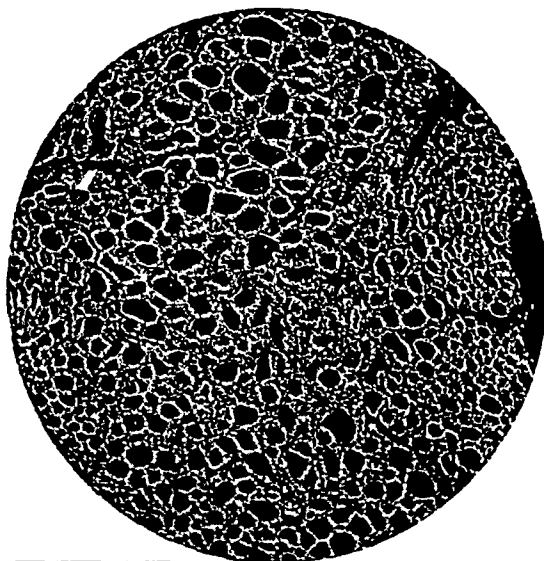
a fairly distinct glycogen loss was determined. The liver glycogen decrease was considerable with an average value of about 36 per cent. According to our previously explained view, a loss of liver glycogen after the injection of anterior lobe occurs only when the thyroid gland is primarily altered. These alterations we could easily demonstrate. Fig. 18 shows the histology of the thyroid gland of an animal which had been injected with this heated substance for seven days. Comparing this with the gland of a normal animal (Plate 2) we see at once the characteristic changes caused by anterior lobe substance (decrease of the stained colloid, epithelial proliferation). That no definite results were obtained in the above cited experiments cannot be squared with our observations. However, it should be noted that our experiments were carried on for a longer time and that larger amounts of thyrotropic substance were used. It is probable that heat destroys most of the activity of the substance. The portion which is uninjured does not suffice to bring about in brief experiments (3 days) a definite change in the thyroid gland. This explains the negative findings. The picture, however, immediately changes if the injections are continued over a longer time. When in this way large amounts are administered sufficient concentration of the substance is finally reached to bring about characteristic changes in the thyroid gland. The accepted thermolability of the thyrotropic substance of the anterior lobe seems verified by our experiments.

VIII. CONCLUSIONS

The intraperitoneal injection of the thyrotropic substance of the anterior lobe of the pituitary gland causes changes in the thyroid gland of the guinea pig morphologically and functionally like those of exophthalmic goiter in man. These changes can be seen two hours after the injection.

The injection of the anterior lobe of the hypophysis results in stimulating the secretion of the thyroid gland. With the development of changes in the thyroid gland the glycogen content of the liver diminishes transitorily. This initial disappearance of liver glycogen is replaced within twenty-four hours after the injection. In spite of advance of the changes in the thyroid gland, the glycogen content of the liver for a time remains constant. Hyperfunction of

FIG. 18



The thyroid gland of a guinea pig treated for seven days with boiled thyrotropic substance. The epithelium of the central acini is distinctly elevated and the colloid has somewhat disappeared. In the peripheral parts of the gland the changes are less distinct. Glycogen content of the liver, 1.5% (Nr. 972).

FIG. 17



Remaining thyroid gland rests in a thyroidectomized animal. The animal received a total amount of 27.5 mg. of anterior lobe substance and was killed 24 hours after the last injection. (Duration of Treatment, 12 days.)

the thyroid and the glycogen content of the liver, therefore, do not run parallel. A continuous decrease in the liver glycogen occurs only after a certain latent period of about four days. The glycogen depletion once begun reaches the highest point sometimes after seven, always after eleven days of injections. At this time the liver is glycogen free.

The glycogen depletion of the liver is a direct result of the hyperfunction of the thyroid gland caused by the anterior lobe of the hypophysis. The changes in the thyroid gland and the glycogen depletion of the liver are reversible. After discontinuing the injections the glycogen content of the liver rises and within seven days nearly reaches its original amount. At the same time the signs of thyroid hyperfunction disappear.

The muscle glycogen shows only unimportant fluctuations during the period of treatment.

The effect of the thyrotropic substance of the anterior lobe of the pituitary in diminishing the liver glycogen occurs only when the thyroid gland is present. The effect does not take place in thyroidec-tomized animals.

Zondek and Ascheim²³ regard the anterior lobe of the hypophysis as the activator of the sexual functions. However, the hypophysis not only regulates the activity of the gonads but also controls other organs of internal secretion, as we have demonstrated for the thyroid. Unfortunately, we have not yet developed methods which will allow us to demonstrate the dominant role of the anterior lobe in the activity of the whole endocrine chain of glands. So far, this role has been established only for the sex glands and the thyroid.

REFERENCES

- ¹EVANS AND LONG: *Anat.Rec.*, 21:62, 1921.
- ²ASCHHEIM AND ZONDEK: *Klin.Wchnschr.*, 7:831, 1928.
- ³ARON: *Compt.rend.Soc.de biol.*, 105:581, 1930.
- ⁴LOEB AND BASSET: *Proc.Soc.Exper.Biol.& Med.*, 27:490, 1930.
- ⁵VERZAR AND WAHL: *Biochem.Ztschr.*, 240:37-49, 1931.
- ⁶JANSEN AND LOESER: *Arch.f.exper.Path.u.Pharmacol.*, 163:517, 1931; *Klin.Wchnschr.*, 10:2046, 1931.
- ⁷LOESER: *Arch.f.exper.Path.u.Pharmacol.*, 163:530, 1931; *Klin.Wchnschr.*, 10:2047, 1931.
- ⁸SALOMON: *Deutsches Arch.f.klin.Med.*, 154:221, 1927.
- ⁹SCHITTENHELM AND EISLER: *Klin.Wchnschr.*, 11:61, 1932.

- ¹⁰ SCHITTENHELM: *Med.Klin.*, 28:275, 1932.
- ¹¹ GRAB: *Klin.Wohnschr.*, 11:1215, 1932.
- ¹² SCHNEIDER AND WIDMANN: *Biochem.Ztschr.* (in Press); *Deutsche Ztschr.f. Chir.*, 236:405, 1932.
- ¹³ LOEB, CLOSS, MACKAY: *J.Biol.Chem.*, 96: 588, 1932.
- ¹⁴ ABELIN: *Biochem.Ztschr.*, 228:167, 1930.
- ¹⁵ ABELIN: *Ibid.*: ABELIN AND KÜRSTEINER: *Biochem.Ztschr.*, 198:10, 1928.
- ¹⁶ FUKUI: *Pflüger's Arch.f.d.ges.Physiol.*, 210:427, 1925.
- ¹⁷ HOUSSAY AND BIASOTTI: *Ibid.*: 227:239, 1931.
- ¹⁸ PFLÜGER: *Pflüger's Arch.f.d.ges.Physiol.*, 129:362, 1909.
- ¹⁹ JANSSEN AND LOESER: *Arch.f.exper.Path.u.Pharmacol.*, 163:525, 1931.
- ²⁰ ARON: *Compt.rend.Soc.de biol.*, 105:975, 1930.
- ²¹ LOESER: *Arch.f.exper.Path.u.Pharmacol.*, 166:693, 1932; *Klin.Wohnschr.*, 11: 1271, 1932.
- ²² JUNKMANN AND SCHOELLER: *Klin.Wohnschr.*, 11:1176, 1932.
- ²³ ANSELMINO AND HOFFMANN: *Klin.Wohnschr.*, 10:2380, 1931.
- ²⁴ FUKUI: *Pflüger's Arch.f.d.ges.Physiol.*, 210:415, 1925.
- ²⁵ SCHOCKAERT: *Proc.Soc.Exper.Biol.& Med.*, 29:307, 1931.
- ²⁶ KLOSE: *Neue Deutsche Chirurgie*, 44:61, 1929.
- ²⁷ VERZAR AND WAHL: *Ibid.*
- ²⁸ VERZAR AND WAHL: *Ibid.*
- ²⁹ CREW AND WIESNER: *Brit.M.J.*, 1:778, 1930.
- ³⁰ JANSSEN AND LOESER: *Ibid.*
- ³¹ LOESER: *Ibid.*
- ³² LOESER: *Arch.f.exper.Path.*, 166:693, 1932.
- ³³ ZONDECK AND ASCHHEIM: *Ibid.*

CONCERNING THE BROADENING OF THE INDICATIONS FOR OPERATION IN EXOPHTHALMIC GOITRE THROUGH THE RECOGNITION AT THE BEDSIDE OF A SECONDARY THYROGENIC INJURY TO THE LIVER*

By DR. ERICH SCHNEIDER, M.D.

Privatdozent, University of Freiburg, Germany

SHORTLY after the surgical treatment of exophthalmic goitre was inaugurated by Ludwig Rehn and Tilieux, the former made the following statement: "Without a diseased thyroid gland no exophthalmic goitre." Early operation for Basedow's disease received at first little acclaim because it was the general impression that the operation was very dangerous. This impression was false. Early surgical statistics are filled with the records of patients who accepted operation only as the last resource and who were therefore in the worst possible condition. Now it is well known that the preoperative use of iodine has greatly reduced the danger of operation, and early operation may now be urged more confidently than ever before. However, in spite of the generally accepted advantage of the present day preoperative treatment—which depends upon the fundamental demonstration at Kocher's clinic of the action of iodine and the elaboration of this principle by Plummer—early operation is still too seldom advised. This has been in some measure due to the prevalent clinical view which pays too much attention to the thyroid gland itself and neglects secondary thyrogenic injuries, particularly those to the liver. These as yet have not received the consideration they deserve no doubt because heretofore the diagnosis of the condition at the bedside has been impossible.

We will assume that the effects of administering substances which act upon the thyroid gland are well known. However, the conclusion that these results represent a genuine thyroid effect may be objected

* From the Surgical Clinic, University of Freiburg, Germany, Dr. E. Rehn, Director.

to on the ground that one important bit of evidence is lacking, namely, the definite histological proof that the thyroid gland undergoes the changes which are characteristic of exophthalmic goitre. This proof is all the more important since it is generally known that thyroxin represents at most only a part of the thyroid hormone and that it does not circulate in the blood stream in the free state as Schneider and Widmann¹ have demonstrated by combustion analysis of the blood.

The isolation of the thyrotropic hormone of the anterior lobe of the pituitary has furnished us with the means of producing changes in the thyroid gland which had not previously been observed. The action of this thyrotropic hormone depends upon the integrity of the thyroid gland. Changes in the thyroid gland produced by the administration of this substance cause glycogen depletion of the liver through an increased secretion of the thyroid gland hormone. (Eitel and Loeser.) When an active thyrotropic substance is administered in proper doses there is at first a latent period, but at the end of this period glycogen rapidly disappears from the liver and at the end of ten days is completely gone. (Eitel and Loeser.) Further observation has shown that when the thyrotropic hormone is administered over too long a period the thyroid gland finally becomes refractory, as may be recognized by careful histological examination of the gland. Some of our experiments showed that most of the animals could take a daily dose of 100 guinea pig units thyrotropic hormone without any bad effects. When these doses are given the follicles of the thyroid gland are completely free from colloid on the tenth day, but when the injections are continued at the same dose colloid begins to re-accumulate on the fifteenth day and the epithelium again becomes flatter. If the injections are continued for a period of three months none of the previous changes can any longer be recognized in the thyroid gland.

The brief cellular stimulation of the thyroid under the influence of the anterior lobe of the hypophysis with its thyrotropic component furnished the possibility of investigating experimentally the damage done the liver by thyroid overactivity. The object was to devise a method which would yield at the bedside a quantitative estimation of the injury sustained by the liver. Under the influence of thyrotropic hormone the liver is totally depleted of glycogen at

the end of ten days. However, such a complete loss of glycogen does not indicate serious liver injury, provided glyconeogenesis is preserved. Therefore, our first object was to discover whether thyrogenous liver damage was more or less identical with toxic liver damage.

The severe alterations which follow intestinal obstruction are characterized chiefly by intense fatty degeneration of the liver and a decided hypochloremia of the blood. The hypochloremia may be regularly demonstrated even when sodium and chlorine are determined separately. It is important to call attention to this, since at times sodium values are not decreased and they never parallel the values for chlorine. In addition to the increase of alkali reserve which regularly occurs in intestinal obstruction Eggs² has recently demonstrated in our laboratory that the potassium in the serum increases by about 50 per cent. From the numerous investigations of Beckmann,³ Seulberger,⁴ Häbler⁵ and others we may conclude that when parenchymatous degeneration of the liver is present sodium and chlorine carried in the portal vein pass through the liver, whereas they are stored by the normal liver. It has not yet been determined whether or not the total sodium and chlorine content of the liver is decreased when such changes are present. However, we may assume that the greater the degree of liver damage the lower will be the content of chlorine which is normally retained by the liver and hardly at all excreted in the bile. At any rate, it is definitely established that chlorine has nothing to do with the binding of toxin.

By following separately the fate of the different ions it has been proved that under the influence of the thyrotropic hormone a definite and decided reduction occurs in the sodium content of the serum and of the liver. The reduction of sodium runs parallel with the loss of glycogen. Table 1, which shows the averages of a large series of experiments, illustrates this. The sodium was determined by the method of Kramer and Fisdall,⁶ Kramer and Gittlemann⁷ modified by Baleut.

A marked fall of sodium having been established further investigations were pursued in two directions. First, the question of transmineralization had to be investigated, especially of potassium on account of its effect upon sympathetic tonus; second, the fatty degeneration of the liver had to be studied further. We began with a

TABLE 1

Average Values for Normal Guinea Pigs Treated with Thyrotropic Hormone

Weight in gr.	Daily Amount Injected in mg.	Total Amount Injected in mg.	Content of the Blood Serum of		Weight of the Liver in gr.	Contents of the Liver in		
			Sodium mg. %	Chlorine mg. %		Sodium mg. %	Chlorine mg. %	Glyco- gen mg. %
273,4	Controls		272,4	466,1	6,08	48,47	169,1	2,26
183,1	5	25	235	330,9	5,76	13,69	155,45	Ø
166,25	5	50	125,59	337,5	6,4	19,1	153,01	Ø
169,3	5	75	110	372,46	5,56	32,27	111,8	Ø
146,6	5	100	123,6	382,7	4,46	9,1	188,27	Ø

consideration of the potassium values, bearing in mind that the action of the vagus is accompanied by a relative increase of potassium. In our experiments increased vagus tone is considered to run parallel with increase of potassium. It may no longer be doubted that the hormones which modify metabolism are carried through the blood stream to the cells upon which they directly exercise their specific effects. These effects occur without the mediation of the vegetative nervous system. Eitel, Krebs and Loeser⁹ have shown that the thyrotropic effect occurs with bits of thyroid tissue in vitro, conditions which eliminate entirely all possibility of the vegetative system playing a part. Our experiments demonstrate that no fall of potassium values occurs under the influence of the thyrotropic hormone. In guinea pigs the normal potassium value for blood serum is about 21 mg. per cent. and the liver contains an average of 247.8 mg. per cent. of potassium. When thyrotropic hormone is given in the usual dose of 100 guinea pig units the potassium in the blood remains unchanged. Even after ten successive days of treatment, when the effects of the hormone are at their height, the serum potassium was found to be 20.6 mg. per cent. and the liver potassium content 247,6 mg. per cent. This demonstrates that no change occurs in the potassium content of blood or liver.

Fatty degeneration of the liver occurs regularly in starvation and in poisoning with many substances, but Abelin, Goldner and Kobori¹⁰ could discover no fatty change in the liver rendered completely

glycogen-free by the administration of thyroid gland even though the muscles showed a marked loss of fat. Indeed, Abelin and Kirsteiner¹¹ have shown that after the administration of thyroid the liver not only loses its glycogen but that it also becomes poor in fat. In a word, fat metabolism is influenced by thyroid gland substance in the same way as are carbohydrate and protein metabolism. Our own observations have demonstrated that under the influence of thyrotropic hormone, even at the height of its action, there is no increase of fat in the liver, that is, fatty degeneration does not occur. We have also shown that there is no diminution in the amount of fat in the liver or in the muscles when thyroid hyperactivity is stimulated. The fatty acid values of the liver, calculated in per cent. of fresh tissue, averaged 0.96 per cent.; after ten days of injections 0.9 per cent. The fatty acid content of muscle was 0.63 per cent.; at the end of the period of treatment 0.79 per cent. The differences lie almost within the range of error of the methods of estimation.

To summarize these observations we may say that thyrogenous liver damage is characterized by a loss of glycogen which is the mark of increased decomposition of carbohydrate. In contrast to toxic damage fatty degeneration does not occur since the law of isodynamic substitution does not here apply. The toxic damage which occurs in ileus is characterized by hypochloremia and hyperalkalinemia while the sodium level is unchanged. The thyrogenic liver damage is characterized by a drop of the sodium level while chlorine and potassium remain unchanged.

Henschen and de Quervain have raised the question whether we are justified in speaking of the glycogen loss of the liver in Basedow's disease as liver damage, particularly since this condition cannot be ascertained clinically. Now that we have established the fact that the loss of glycogen is accompanied by a fall of the sodium level in the serum the changes in the liver can be followed by the simple procedure of drawing a little blood from the patient at the bedside.

At the recent meeting of the International Goitre Congress at Berne Eppinger suggested that it might be possible to estimate accurately the severity of Basedow's disease by determining the iodine content of the blood since it has been shown that the amount of iodine in the blood is always increased in Basedow's disease. This suggestion cannot be put into practice because the methods now used to

determine blood iodine are unreliable. There is still a wide difference of opinion about the amount of iodine in normal blood. By using an improved method we find, in contrast to most authors, that the normal iodine level of the blood is higher than is usually stated. We find an average amount of 32 mg. per cent.

If we follow the level of iodine in the blood we find that following the administration of the thyrotropic hormone, after a latent period of from three to four days, an increase of iodine occurs, but that when the hormone is continued the iodine begins to fall and after a certain period reaches a lower level than was originally present. This fall may perhaps be explained by assuming that under continued stimulation the thyroid may become exhausted and have no more iodine to deliver to the blood.

From these experimental results we may be able to draw helpful suggestions about treatment at the bedside. It has been generally thought that the serious symptoms which sometimes follow operation upon exophthalmic goitre, and occasionally prove fatal, are due to manipulation of the gland causing a sudden discharge of large amounts of secretion. Some observers reported finding drops of colloid in the veins and advanced this observation to substantiate the view. In conformity with this view special care was exercised in developing an operative technic that avoided the least trauma to the gland and it would be regrettable were this operative care ever abandoned for it has far reaching consequences in relation to operative shock. (E. Rehn,¹⁴ E. Schneider.¹⁵)

We will not here consider the operative technic. Enderlin¹⁶ has recently discussed the operative procedure generally used in Germany. However, in spite of the most careful technic postoperative death cannot be completely eliminated. The attempt to demonstrate definitely that following operation the organism is flooded with thyroid secretion has not succeeded. Indeed, Bier and Roman,¹⁷ on the basis of blood iodine estimations, come to the conclusion that there is more of a hypo- than a hyperthyroxemic shock. Rahn¹⁸ has recently demonstrated that in Basedow's disease the postoperative elevation of basal metabolism is about 16 per cent., an increase in no way characteristic of Basedow's disease since the same elevation is observed after the removal of ordinary goitres and even after operations on organs other than the thyroid. In many instances

the elevation may be explained by postoperative fever. These facts seem to make it clear that death following operation upon the thyroid gland in Basedow's disease is not essentially due to a sudden outpouring of thyroid secretion. It is much more likely that the cause resides in the secondary changes produced by hyperthyroidism. The thyrogenic heart and liver alterations are no doubt the most important. We must admit that it is impossible to determine the liver damage definitely and specifically by the use of glucose tolerance tests.

The benefits of a thorough preoperative treatment with iodine are well known. The difficulty encountered in some cases may best be illustrated by asking: "What are we to do with patients who fail to react satisfactorily to iodine, whose basal metabolic rate does not fall?" Up to the present time it has been advised to discontinue iodine and after a few weeks of conservative treatment to make another effort to get the desired results. We take exception to this practice and ask if there are really cases of exophthalmic goitre which are refractory to iodine.

The basal metabolism has been the clinical criterion by which we have gauged the effects of iodine. These results have not been controlled by histological examination of the thyroid gland. The patients who fail to show a fall of the basal metabolic rate are seldom operated upon and therefore we do not have an opportunity to examine the thyroid gland. In testing out a large number of substances which have an effect antagonistic to that of thyroid we found without exception that no matter what their chemical composition may be, provided they contain iodine, they produce an increase of colloid in the thyroid gland.

It seems probable that so-called refractory cases respond to iodine with an increase of colloid but that the secondary changes are so far advanced a fall of the basal metabolic rate does not occur. These facts and this interpretation are illustrated in Table 2.

The histological examination of the thyroid glands removed at operation, for which we are indebted to Professor Aschoff, shows in nearly all the condition spoken of as "basedowification" which may be accompanied by all the symptoms, including exophthalmos, of true Basedow's disease. However, Aschoff has emphasized that with "basedowified" goitres one never observes the proliferation of lym-

TABLE 2

No	Name	Age	Race	Basal Metabolic Rate	Basal Metabolic Rate After Lugol Solution	Basal Metabolic Rate After Operation	Histological Diagnosis
1	A.	48	M.	+80	+30	+10	Struma nodosa colloides resembling Basedow.
2	H.	38	M.	+50	+10	+5	Struma colloides microfollicularis.
3	G.	30	W.	+77	+40	+5	Small follicular colloid struma.
4	G.	40	W.	+71	+40	+15	Struma nodosa, parenchymatosis
5	R.	23	W.	+40	+22	-2	Struma diffusa, basedowificata
6	M.	43	M.	+72.8	+20.3	-4.96	Basedowstruma, epithelial elevation.
7	P.	53	W.	+62	+66	+20	Struma nodosa, rich in colloid proliferation.
8	R.	27	W.	+77	+66	+25	Basedowstruma, tightly packed colloid.
9	M.	37	W.	+90	+70	+7	Struma nodosa parenchym, deficient colloid content (Iodine basedow-clinical).

phoid tissue and the characteristic enlargement of the thymus which occurs with genuine exophthalmic goitre.

Patients 7, 8 and 9 of Table 2 are three typical instances of refractoriness to iodine, that is, the basal metabolism fell little or not at all after the administration of iodine. These cases present a difficult problem from the stand-point of treatment and for them especially we need a broader indication for operation. Clinical experience and theory founded upon experimental facts emphasize this need. Clinical experience teaches us that operation is often well borne even though the basal rate may be high, provided that the operation is promptly undertaken. If operation is long deferred and conservative treatment persisted in the patient's general condition grows worse if the basal rate does not fall.

We may point out further that when the anterior lobe of the hypophysis is given to patients the basal metabolic rate may rise to +50 or +60 and yet no other clinical manifestations occur. Occasionally a slight bruit may be heard over the thyroid gland, but in contrast to patients who have been ill for some time with exophthalmic goitre there are no symptoms which might lead one to suspect that the basal metabolic rate was greatly increased. From this we may conclude that the height of the basal metabolic rate and the pulse are not alone safe guides to the condition of the patient. The

INTERNATIONAL CLINICS

Supplement June, 1934

Clinical Case Studies

FROM THE RECORDS OF THE
PITTSBURGH DIAGNOSTIC CLINIC

3509 FIFTH AVE.

PITTSBURGH

FOREWORD

The object of these studies is to afford practice in the formulation of a diagnosis on the basis of the history and physical findings, together with such technical procedures, X-ray studies, and opinions of specialists as may seem to be indicated. Actual case records are used, unchanged except for the deletion of identifying names and such editing as may seem advisable for the sake of brevity and clearness.

DIRECTIONS

Proceed on the basis that each case is a patient under your own care. The general history and physical findings as printed in this supplement represent what you would learn from the first visit of the patient in your office. After studying these make up your mind as to the most likely working diagnosis and put this in writing in the space provided for "Notes", this being solely for your own reconsideration in light of later information. Select the enclosed post card correspondingly numbered with the case problem you are studying and check off on the card the special procedures which you feel are definitely indicated; do not ask for everything blindly, but for only such studies as you would order if this were your own private patient. Mail the card promptly to the Pittsburgh Diagnostic Clinic, making certain to show your name and address.

You will receive from the Clinic two packets for each case. In one, will be the information you requested, provided it is available. Study this material and make up your mind as to the final diagnosis, putting your opinion in writing on the page provided for "Notes". Then open the second packet which contains the final report made by the Clinic Staff, and follow-up information as to the patient's subsequent clinical course which serves as a check on the accuracy of the diagnosis.

It is particularly urged that you commit yourself in writing at every stage of the study because a comparison of the provisional with the final diagnosis will frequently prove most instructive.

GENERAL HISTORY

White Male Married Age 36 years

CHIEF COMPLAINT

Lack of energy.

Itchy eruption on the legs below the knees.

PRESENT ILLNESS

For the past year and one-half the patient has noticed gradually increasing lack of energy; he feels tired and "lacking in muscle tone," so that it is an effort for him to physically exert himself. There is poor appetite in the morning, which improves throughout the day so that toward evening he usually enjoys a very large meal. At occasional intervals, however, there will develop a sudden sensation of nausea immediately after eating so that he may vomit the entire meal; no constant gastro-intestinal disturbances and no diarrhea or severe constipation; no urinary symptoms.

In addition to his tiredness and lack of energy, his physician has found a low blood pressure, averaging 90, for the past year. Both he and his friends have noticed a change in his appearance, this being due mostly to a slight puffiness of the face and a tendency to yellowish complexion, although there has been no true jaundice. His hands, also, feel puffy and stiff, and his fingers are larger, so it is difficult to wear a ring which was formerly comfortable. He, himself, is conscious of the fact that he thinks and speaks more slowly. There is a tendency to chilliness, especially when the weather is cool.

Two weeks ago he began to be bothered with itchiness of both legs below the knees, together with the development of peculiar localized skin lesions, appearing first as an area of redness, then itchiness, with a white center, this rapidly developing into a

blister which showed a tendency to become larger and larger. At the present time his legs show eight or ten such lesions in every stage from the area of erythema to that of localized induration and itching and then various blisters with yellowish clear fluid, and finally the residual stage where the water has either been reabsorbed or mechanically discharged, with the loose, dead skin lying close to the under surface. In relation to this it may be significant that the patient has suffered with the Fall type of hay fever all his life, and that just before the development of the eruption on the legs he walked through a field that was thick with ragweed in pollen.

PAST HISTORY

Recurring attacks of tonsillitis by reason of which the tonsils were removed one year ago. No rheumatism. He also had a severe influenza in 1910 while in the army, being delirious for several days and incapacitated for two or three weeks. No other acute illness. No trouble with the eyes, ears, nose or throat, except for the recurring tonsillitis noted above.

The patient has had two attacks of sudden severe cramp-like pain in the left lumbar region, developing while walking, giving rise to total incapacity, but not associated with any urinary disturbances; both attacks suggested an acute lumbago. The first attack was three years ago, as the result of which he was confined to bed for two weeks. The second attack was last April and disappeared three days after the onset. There is no aching or discomfort in the affected region between these attacks. No symptoms in the past referable to the heart, lungs, gastro-intestinal, or genito-urinary tracts.

Occupation—Teacher in the Department of Agriculture and this work takes him outside for a considerable portion of his time.

Habits—regular as to hours of eating and sleeping; no alcohol. Tobacco, very moderately.

Venereal history—negative.

Marital history—married, wife living and well; one child living and well.

Family history—negative.

PHYSICAL EXAMINATION

GENERAL

Height 67½ inches Weight 147 pounds Temperature 98°

Patient is normally developed, rather slow in his movements; seems a little listless, but there are no signs of mental depression or emotional instability. Skin is not noticeably dry, but the hair of the scalp is sparse. There is a distinct yellowish brownish pigmentation to the face, but this does not involve the skin of the body. There is also a slight, brawny, generalized subcutaneous edema, not pitting on pressure.

HEAD AND NECK

Ears—negative. Eyes—pupils are equal, react normally, associated movements normal. Mouth—teeth are well preserved, gums clean. Throat—not injected, tonsils well removed. Glands—no general enlargement; thyroid—not enlarged.

THORAX

Lungs are clear throughout.

Heart—normal size, rate is 68, regular in force and rhythm; sounds are somewhat distant, soft, but no murmurs are heard; pulse—68, regular, no abnormal thickening of vessel wall.

ABDOMEN

No masses or areas of tenderness; spleen not felt; liver to costal margin, edge not felt.

EXTREMITIES

Slight, brawny edema; reflexes are all normal, no tremor. Fingers are puffy in appearance, but there is no thickening of the joints or other abnormality. Scattered over both legs below the knees are various stages of bullous-like eruptions, varying in size from 5 to 10 mm., tending to be confluent, the earliest ones being round erythematous areas, itchy, with a white, fairly indurated center. Later ones are round circumscribed blisters, raised up, with clear yellowish contents, but no signs of inflammatory reaction about the periphery.

BLOOD PRESSURE

Systolic, 85. Diastolic, 50.

NOTES

MY PROVISIONAL DIAGNOSIS

Based on History and General Physical Examination only.

MY REVISED DIAGNOSIS

Taking into consideration reports requested on special studies.

GENERAL HISTORY

White Female Married Age 58 years

CHIEF COMPLAINT

Recurring cramp-like pains in the midepigastrium.

Vomiting of blood and passage of tarry stools.

PRESENT ILLNESS

Onset about two months ago when she began to be bothered with severe, recurring, cramp-like pains high up in the midepigastrium, associated with sensations of gas, eructations of sour burning material and occasional vomiting. When she would vomit the material was very sour and on several occasions contained small amounts of moderately bright blood. There was also a bad taste in the mouth and a bad, nauseating taste to the material she would eructate. She noticed at occasional intervals that her stools were "black as coal." The cramp-like pains were more or less constant, but were accentuated if she took anything into the stomach, even water, with the single exception of milk of magnesia which would accord her temporary relief. When the stomach was empty the pain was less marked, but was not entirely absent. These sensations continued becoming more and more marked until five days ago when, while cooking her noon meal, she suddenly became faint and finally fainted. She revived almost immediately, but felt very weak. She noticed that the severe pain in the midepigastrium had disappeared, and this has not recurred to any noticeable degree up to the present time. The next day after she had fainted, she vomited a rather large amount of coffee-ground material, and since then her stools have constantly been black and tarry. She feels very weak. In regard to weight, the information is unsatisfactory. There has apparently been a moderate loss of weight in the past year, but

NOTES

MY PROVISIONAL DIAGNOSIS

Based on History and General Physical Examination only.

MY REVISED DIAGNOSIS

Taking into consideration reports requested on special studies.

twenty-two years ago she was operated upon for rectal fistula since when there has been no recurrence of any such signs. She had pneumonia twenty years ago; otherwise, past history is quite negative.

No particular symptoms referable to the eyes, ears, nose, throat, heart, lungs, gastro-intestinal, or genito-urinary tract except those outlined above.

Marital history—married 37 years; three children, ages 34, 31 and 26, all living and well. Had two or three miscarriages, one at six and seven months, between the second and third children; no pregnancy since the third child. Husband is living and well.

Habits—regular as to hours of eating and sleeping.

Family history—father suffered with chronic rheumatism and finally died of so-called "rheumatic heart." Otherwise, family history is negative.

PHYSICAL EXAMINATION

GENERAL

Height 63 inches . Weight 145 pounds Temperature 98.6°

Patient is of the robust, stocky, short-necked type; she appears somewhat pale and there is a very slight yellowish tint to the skin; no cyanosis, jaundice, eruptions, or evident dyspnea. Patient does not present the usual appearance of cachexia. The skin is of normal texture and the subcutaneous fat is well preserved.

HEAD AND NECK

Ears—negative. Eyes—pupils are equal, react normally, associated movements normal. Mouth—teeth all out except for the lower front; gums are clean. Throat—tonsils well removed. Glands—no supraclavicular nodes; no general enlargement. Thyroid—not enlarged.

THORAX

Lungs are clear throughout.

Heart—moderately enlarged down and to the left; point of maximal impulse is in the fifth interspace, just in mammillary line; rate is 90, regular in force and rhythm. Sounds are rather blurred, somewhat indistinct, but no murmurs can be heard. Over the aortic area the aortic second is rough and accentuated, but there is no definite murmur. Pulse—90, regular, no abnormal thickening of vessel wall.

ABDOMEN

There is distinct, persistent tenderness high up in the midepigastrium, making deep palpation rather unsatisfactory; palpation is not attempted with great pressure because of the history

of a recent gastric hemorrhage; no mass can be felt; liver is palpable one finger's breadth below the costal margin, but it is of normal consistency and no tenderness is made out; no tenderness in the liver region. No tenderness in the lower abdomen, although the patient complains of soreness of the entire intestinal tract.

EXTREMITIES

No edema; there is distortion, thickening, and some limitation of movement of all the joints of the fingers and toes; no redness or local heat. Some limitation of motion in the hip joints, but no great thickening and no signs of any local disease. No tremor.

BLOOD PRESSURE

Systolic, 185.

Diastolic, 90.

NOTES

MY PROVISIONAL DIAGNOSIS

Based on History and General Physical Examination only.

MY REVISED DIAGNOSIS

Taking into consideration the reports requested on Special Studies.

degree of secondary changes in other organs, especially those in the liver, must be determined to give us a better understanding of the patient's real condition.

This gap in our knowledge may not be filled by making a single determination of the sodium in the blood serum which, as previously explained, is an index to the degree of liver damage. As shown in Table 3 the sodium level in the blood serum is relatively constant,

TABLE 3

SODIUM CONTENT OF THE SERUMNormal

No.	Name	Diagnosis	Sodium in mg%
1	Sch	Paronuchia	281.8
2	R	Oral sepsis	309.0
3	K	Cervical Fistula	247.0
4	B	Furuncle	250.1
5	B	Cervical Phlegmone	284.1
6	M	Healthy	248.4
7	K	Healthy	293.3
8	D	Ulcer on thigh	272.0
9	B	After Struma-operation	290.0
10	Z	After Struma-operation	323.0
AVERAGE			281.9

Basedow

No.	Name	Diagnosis	Sodium in mg%	Basal metabolic rate before operation
1	S	Coma basedow	195.0	—
2	H	Basedow	74.0	+71
3	P	Basedow	134.0	+66
4	S	Basedow	53.0	+65
5	M	Iodine Basedow	138.5	+70
6	H	Basedow	162.0	+56

the average being about 281 mg. per cent. Bedside observations confirm what was found experimentally. Patients with hyperthyroidism or Basedow's disease show a more or less marked fall in sodium values and the fall bears no constant relation to the height of the basal metabolic rate. This is easily understood when we remember that the fall of sodium is only an indication of thyrogenic liver damage. The degree of the fall will be less the earlier the patient is properly treated.

Since we need not fear a sudden postoperative flooding of the circulation with thyroid secretion and since a high basal metabolic rate is not a sign of great danger, provided there is no evidence of serious damage to the liver or the heart, we may now confidently widen the indications for operation. However, it is important to determine whether in connection with postoperative improvement the sodium values rise again to the normal level. This is precisely what happens. To give an example, in a patient with typical Basedow's disease the basal rate was $+56$ per cent., the sodium of the blood serum 162 mg. per cent.; eight days after operation sodium had increased to 234 mg. per cent. This indicates that when the harmful agent is removed the damage done the liver may soon be repaired.

According to our observations a value of 100 mg. per cent. is the lowest level to which the serum sodium can fall without there being the gravest danger attached to operation. It is very important, therefore, in Basedow's disease that in addition to estimating the basal metabolic rate, taking an electrocardiogram and making the other usual observations, we should also determine the sodium content of the blood serum. If the sodium value is above 100 mg. per cent. and reaches 200 mg. per cent. we may then safely advise operation even though the basal metabolic rate may fall but a little after giving appropriate doses of iodine. As may be seen in Table 2 patients 7, 8 and 9 were operated upon although the basal metabolic rate fell but little. Nevertheless, the results were altogether satisfactory thus demonstrating the truth of what has been said.

We may disregard the question whether a genuine exophthalmic goitre is ever due to the ingestion of iodine. Clinically the diagnosis is made upon the history. If a nodular struma is rendered active by the use of iodine the patient reacts; indeed, he may respond with an increase in basal metabolic rate and secondary manifestations in spite of careful treatment carrying on for years. Plummer. Delay will then cause the disease to become more and more severe. A determination of the early operation and the extent of the damage is on the basis of the reduced we will observe the damage and operation. Iodine treatment; indeed, secondary manifestations in relation to the disease become the extent of the damage to the sodium metabolism. Iodine treatment; indeed, secondary manifestations in relation to the disease become the extent of the damage to the sodium metabolism.

though the basal metabolic rate may be as high as 70 per cent. Therefore, it is possible with this method to give some objective support to subjective clinical impressions and in this way to increase the security with which operation is undertaken.

If these methods have made it possible to establish a definite indication for operation, then the experimental methods have also made possible a more thorough, critical appraisal of the value of the various preparations used in preoperative treatment. As previously mentioned, these studies have demonstrated that iodine in any form deposited upon the thyroid gland and increases the colloid.

The further development of preoperative treatment was concerned with finding substances which will counteract the thyroid-induced liver damage so that iodine may be reserved for use immediately before operation. Recently, Vitamin A has acquired some reputation in this connection since it has been shown that Vitamin A will counteract the effects of thyroxin upon rats in equimolar doses. In our experiments we found that Vitamin A does not act directly upon the thyroid gland since the histological changes caused by the stimulation of the thyrotropic hormone are in no way altered. Nevertheless, it is possible in a limited way to diminish the harmful effect upon the liver. The glycogen depletion of the liver and the fall in serum sodium can be partly hindered by Vitamin A. When Vitamin A alone is administered we find, as have also Bomskow and Sammann,²⁰ that liver glycogen is much increased although the blood picture and nonprotein nitrogen values are unaltered. By combining Vitamin A with a preparation of liver, for instance Campolon, we have at hand a method with which we can influence thyroid-induced liver damage without the use of iodine and without fear of dangers attending its use. This simplifies the preparation of patients for operation since iodine may be dispensed with. We have also tested experimentally the value of carotin. Carotin is changed in the liver almost quantitatively into Vitamin A. Using a preparation named "Vogan" we could detect no difference in action from that of Vitamin A. Therefore, there is no evidence to show that under the influence of thyrotropic hormone the ability of the liver to transform carotin into Vitamin A is to the slightest degree impaired.

neglected by many assuming responsibility for the treatment of pulmonary tuberculosis.

When sufficient functional relaxation of the lung cannot be produced by bed and postural rest alone, additional rest by collapse or compression of the lung in selected cases should be provided by resorting to collapse therapy procedures.

Under the title "collapse therapy" is included a number of methods, the purposes of which are to place a part or the whole lung at functional rest and close cavities in order that healing may take place. This is accomplished by collapse or compression of the lung by methods directed to the lung itself or indirectly by collapsing the chest wall through the resection of rib.

While collapse therapy includes many procedures proposed to accomplish the above purpose, only those methods which have a sufficient background of experience to remove them from the experimental field will be discussed here.

At least four of these procedures already have won general approval, namely artificial pneumothorax, intrapleural pneumolysis, phrenic neurectomy and thoracoplasty. Other surgical measures are of value in a few selected cases. If the number of contributions to the literature is any index, one must say that the rôle of surgery in the treatment of pulmonary tuberculosis is becoming more and more appreciated. While phthisiotherapeutists admit the rôle of "collapse therapy," unfortunately, there are too many institutions wherein collapse therapy has advanced little beyond the pneumothorax era.

ARTIFICIAL PNEUMOTHORAX

Artificial pneumothorax is the oldest, best known, most valuable and most widely employed method of inducing lung collapse. It should however be utilized much more often and very much earlier than it generally is. It is indicated in cases of pulmonary tuberculosis with even beginning infiltration and positive sputum, as well as in moderately advanced cases, if, after three to five months, the disease is progressive or not making satisfactory response to the basic "triad,"—at least, it should be employed before destructive lesions have become established.

Hemoptysis of tuberculous origin is an obligatory indication.

FIG. 1

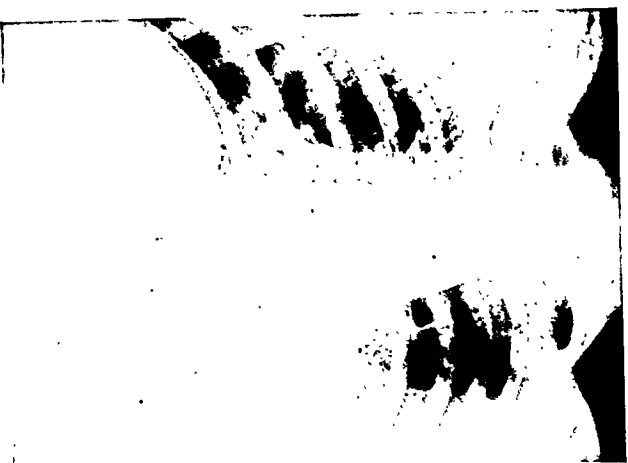


FIG. 2



FIG. 3



Case 7463
Fibrous cavernous tuberculosis right upper lobe with fresh bronchogenic extension lower lobe left lung. Sputum 40 cc. Tubercle bacilli positive.

Same case as Figure 1 approximately six months later. Pneumothorax established on the left side. No cough or expectoration. Sputum negative for tubercle bacilli one month.

Same case as Figures 1 and 2. Two and one-half years later. Lung fully expanded. Pleura very much thickened following serofibrinous exudate. Cavity in right lung entirely healed. Patient working full time. Apparently well.

Tuberculous pleurisy with effusion should be aspirated, the fluid replaced with air and the pneumothorax maintained as long as the underlying disease demands collapse of the lung. Likewise, tuberculous spontaneous pneumothorax should be converted into a controlled pneumothorax. If the disease is advanced to cavity formation, a pneumothorax ought to be induced immediately, for the sooner this is accomplished and the walls of cavities are brought together so that healing may take place, the imminence of disease extending into the other lung, gastro-intestinal tract and larynx is lessened. Confinement of disease to one lung is not a requisite, nor is the presence of even active disease in the opposite lung a contra-indication, providing it is not too extensive or of a rapidly advancing character. When a more or less stationary cavity exists on one side, with an actively advancing metastatic extension in the opposite lung, the pneumothorax should be induced on the metastatic side. Closure of the cavity in the contralateral lung can often be effected if the mediastinum is labile (Figures 1, 2 and 3). We have seen excellent results frequently obtained by pneumothorax in tuberculous pneumonia and bronchopneumonia, if a satisfactory collapse could be provided.

Bilateral pneumothorax is indicated in carefully selected cases, when not too extensive or rapidly advancing disease exists in both lungs, or when a pneumothorax has been established on one side and the contralateral lung disease becomes progressive, but both sides should not be started simultaneously.

The contraindications for artificial pneumothorax comprise co-existence of renal or cardiac failure, or uncontrolled tuberculosis of the larynx or intestines, which seriously interferes with the patient's nutrition, or other irremediable coexistent disease.

Citing our experience of more than twenty years (during which time approximately 1700 cases of pulmonary tuberculosis were subjected to artificial pneumothorax), the end results, excluding economic and environmental problems, were influenced by the type of the disease, and status of the contralateral lung, but the dominant factor was the character of the pneumothorax.

Reviewing the series of 600 cases during the first twelve years of our work, over 40 per cent. of failures were caused by pleuritic

vent the establishment of a satisfactory pneumothorax. This brings one to a consideration of the methods of dealing with adhesions in an effort to provide a satisfactory collapse of the lung by pneumothorax.

INTRAPLEURAL PNEUMOLYSIS (SEVERING ADHESIONS BY THE CLOSED METHOD IN AN ARTIFICIAL PNEUMOTHORAX)

Obviously, if the offending adhesions are diffuse and widespread, permitting only a small pneumothorax pocket, no surgical approach to sever them is safe or likely to be effectual. However, if the pneumothorax is a substantial one, and clinical and roentgenological findings indicate adhesions preventing a satisfactory collapse or compression of the lung, one should consider severing the adhesions. An open operation for this purpose should not even be contemplated, notwithstanding the fact that many thoracic surgeons still advocate it. The authors believe that adhesions which cannot be cut by the open method can be severed very safely by the closed one, and if an attempt were made to do so by the open operation, it would prove a very hazardous procedure,—also, the intricacies of the open operation are so manifold that it is likely to be a shocking one to the patient, being invariably followed by a trail of complications. These unpleasant aspects are totally precluded by the closed intrapleural pneumolysis, which is not dangerous when properly performed. Therefore, the operation of choice is the closed method proposed by Jacobaeus and modified by one of us (R.C.M.). Our mortality in 249 cases is 1.5 per cent.,—this includes also the use of the galvanocautery. This single operative mortality was only indirectly due to the operation. (See note later.)

Preliminary to operation (executed under local anesthesia) one must be well orientated regarding the position of adhesions by careful study of stereoscopic and roentgen lateral films. The patient is prepared preoperatively as for a major thoracic operation,—but the procedure is a very minor one as far as the patient is concerned. After local anesthesia infiltration of 10 to 20 cc. of 1 per cent. novocain suprarenin solution of the intercostal space selected for approach, a one centimeter incision is made and an Unverricht thoracoscope introduced through the chest wall by means of the author's bakelite cannula, at a point affording the most accurate view of the adhesion. This area will usually be in the region of the

angle of the scapula. After thoracoscopic study of the pneumothorax cavity a site is selected for introducing the operating instrument—one that will permit greatest facility for severing all offending adhesions. The operating instrument is also introduced through the small chest-wall puncture, after infiltration with local anesthesia.

One of us (R.C.M.) has recently successfully severed a section of the phrenic nerve under thoracoscopic guidance with a specially designed instrument which can be inserted through the cannula for the operating electrode. The case was one presenting a type of pleuritic adhesion found inoperable upon thoracoscopic study, and where a phrenic neurectomy was indicated. The operation was easily executed by the intrathoracic route, a section of the nerve being removed at a point where it passed over the pericardium. This procedure offers possibilities in certain cases. The method will be fully detailed in a later communication.

According to the technic of Jacobaeus', the intrapleural pneumolysis operation is done with a galvanocautery,—whereas we employ a high-frequency current (Bovie Unit*) for cutting, with special electrodes† designed by one of us (R.C.M.). By this method the disagreeable characteristics accompanying the introduction of a heated cautery into the pleural cavity are completely absent: there is only very slight or no reaction at all to the operation, and little or no pain. The author's electrosurgical method is transcendent over the galvanocautery in that the operation is executed more quickly, with the danger of complications greatly minimized.

The indications for intrapleural pneumolysis are as follows: In the vast majority of cases selected for pneumothorax treatment, adhesions will be present in almost half of them, but they will not prevent a satisfactory collapse or compression of the lung. Therefore, the mere presence of adhesions is no indication for operation. However, if, after a reasonable trial of pneumothorax therapy (three to five months), there is roentgenological and clinical evidence that adhesions are preventing a satisfactory collapse of the lung, and recovery is jeopardized by continuation of the unsatisfactory col-

* Manufactured by The Liebel-Flarsheim Co., 303 West Third St., Cincinnati, Ohio.

† Manufactured by Mr. Carl McKissick, 425 S. E. 8th Ave., Portland, Oregon.

lapse, intrapleural pneumolysis is indicated. But there should be reasonable assurance that recovery will take place after a satisfactory pneumothorax has been established. It is essential that the pneumothorax be sufficiently large to permit manipulation of the instruments and that the adhesions are of a type appropriate for operation. The operation is also indicated even if, in spite of adhesions, the pneumothorax is a satisfactory one but high intrathoracic pressure is necessary to maintain the collapse, causing pain or coughing paroxysms due to traction, with consequent danger of tearing the adhesions,—hence, resultant spontaneous pneumothorax and empyema. Likewise, if, in the above type of case, the intrathoracic pressure necessary to maintain collapse causes uncomfortable pressure phenomena, such as circulatory disturbance from altered position of the heart or mediastinum, or mediastinal hernia, which frequently defeats the purpose of pneumothorax, the operation should be considered. In efforts to maintain a proper collapse in the presence of adhesions, downward pressure upon the stomach and liver often causes uncomfortable symptoms; these, however, are relieved by severing the adhesions. An additional indication for operation is constituted by adhesions which have become fibrous and are contracting, pulling out the lung and causing an early expansion, often accompanied by increased sputum with reappearance of tubercle bacilli in the sputum, or hemoptysis.

CONTRAINDICATIONS

The contraindications are the same as for the establishment of a pneumothorax. In addition, acute pleuritis is a contraindication. Operation should be deferred until there is no reaction following aspiration. Chronic or afebrile pyothorax is no contraindication.

SELECTION OF CASES

This should be done by a painstaking study of the clinical record, including all laboratory data and a careful review of all the roentgenological findings, with a final study of stereoscopic films made twenty-four hours before operation.

The possibility of operation and the probability of success will often be revealed only by thorascopic examination, which is not

associated with danger. The technic of the operation has been fully covered in previous publications.^{1, 2, 3, 4}

Before considering the complications and end results, a brief description of the various types of adhesions commonly met with, according to our classification, will be given (see frontispiece):

A. *Arachnoid adhesions*.—These, when recent, separate readily without cutting. They never contain lung tissue and are not of technical importance.

B. *String adhesions*.—These are usually round but sometimes flat; some are elastic and fragile, but seldom vascular. As a rule, only a slight increase is seen in their diameter at the chest wall and lung attachments. Their clinical importance is insignificant except when numerous and fibrous.

C. *Cord adhesions*.—This form has the same characteristics as the former group, only they are larger, and while essentially round, at times show ridging. The thoracic wall and lung attachments are often slightly broadened, especially when short, and might be then mistaken for spool or capstan adhesions. They are seldom highly vascular but are of technical importance, as one cord adhesion will often frustrate a satisfactory collapse of the lung.

D. *Band adhesions*.—These adhesions vary greatly in length, thickness and breadth. Lung tissue is seldom found in them but sometimes blood channels of considerable size are encountered. This type is of great technical importance. Aside from bleeding, severance, which should be made close to the chest wall, is not dangerous.

E. *Fan-shaped adhesions*.—This form has a small lung attachment but has wide adherence to the chest wall; small blood-vessels are often contained in the free edge. The transition between lung tissue and adhesion is clearly defined. They rarely contain lung tissue and should be severed near the lung attachment. Cutting them is quite safe and a good therapeutic result follows. (This is the only type of adhesion which should not be severed at the chest wall.)

F. *Funnel or cone-shaped adhesions*.—This type commonly occur over superficial cavities, in which case the cavity is often projected into the adhesion. Cutting them, unless around the chest wall attachment, is dangerous.

G. *Spool or capstan adhesions*.—These contain blood channels of marked importance,—also, prolongations of cavities. The pul-

monary half always contains lung tissue. Although they are less dangerous to cut than the funnel type, the operator should beware of the same hazards and sever this type of adhesion near the chest wall.

H. *Fold and curtain adhesions.*—While frequently appearing as bands on stereoscopic films, giving the impression of being easily cut, fold and curtain adhesions are mostly inoperable, except when thin. They should be severed by indirect illumination.

I. *Diffuse adhesions.*—In this type, the lung is densely adherent to the chest wall. More failures in pneumothorax are chargeable to these adhesions than any other kind and they must not be severed. Occasionally, fold extensions may be severed and the collapse improved.

COMPLICATIONS

Table 1 will reveal the complications occurring after operation in our entire series of 249 cases. But it should be pointed out that the first 136 cases were done with the galvanocautery, and of the remaining 113 cases, thirty-five were performed with several unnamed high-frequency apparatus which provided a cutting current, yet possessed no dehydration qualities; whereas, the last seventy-eight cases were operated upon with the Bovie Unit. Table 2 shows the marked reduction in exudate formation incidence following use

TABLE 1 *

Complications after Operation, Including the Galvanocautery and Author's Method

— 249 Cases —

Serous exudate.....	63—25.7	per cent.
Purulent exudate.....	41—16.5	" "
Hemorrhagic exudate.....	26—10.4	" "
Febrile reaction.....	7— 2.4	" "
Severe hemorrhage.....	3— 1.2	" "
Bronchopleural fistula.....	4— 1.6	" "
Spontaneous pneumothorax.....	1— .4	" "
Severe postoperative vomiting.....	1— .4	" "
Gas embolism.....	0	
Shock.....	0	
Severe surgical emphysema.....	0	

* This table comprises complications occurring in 136 cases operated upon with the galvanocautery and 113 cases operated upon by the author's method. However, in 35 of the latter group, several unnamed high-frequency apparatus were used, while in 78 cases the Bovie Unit was employed.

TABLE 2

Comparative Frequency of Exudate Formation Following Various Operative Methods

— 249 Cases —

JACOBÆUS METHOD		AUTHOR'S METHOD	
	Galvanocautery	Unnamed High Frequency Units	Bovie High Frequency Unit
	136 Cases	35 Cases	78 Cases
Serous exudate.....	28—20.5%	11—31.4%	3—3.8%
Purulent exudate.....	36—26.4%	4—11.4%	2—2.5%
Hemorrhagic exudate.....	14—10.3%	11—31.4%	1—1.2%

of the Bovie Unit. Of three instances of severe hemorrhage, one occurred during use of the galvanocautery and two during operation with the unnamed high-frequency machine. The single instance of spontaneous pneumothorax occurred on the contralateral side seven days after operation; it was due to an asthmatic paroxysm and terminated fatally. This case represents the only fatality in the entire series and was only indirectly due to operation.

RESULT OF TREATMENT

During the past seven years, 311 operations have been performed on 249 cases (Table 3). In 211 cases a single operation was done; in twenty-two cases, two, and ten cases had three operations; four cases had four operations, and two cases had five operations each.

In estimating the value of the operation it must be borne in mind that the purpose of the operation is to convert a useless or unsatisfactory pneumothorax into an efficient one. Accordingly, the results of operation have to do, primarily, with the number of unsatisfactory pneumothorax cases which were converted into satisfactory ones, and remotely to the end-result of the pneumothorax thus established. Every case classified as "clinically and technically successful" from the standpoint of the operation, means that complete severance of all adhesions was effected, followed by a satisfactory pneumothorax with prompt (sometimes immediate) disappearance of severe cough and expectoration.

Of the 249 cases, one hundred and fifty-two, 61 per cent., were

TABLE 3
Intrapleural Pneumolysis
Remote End-Results of Operation
— 249 Cases —

— 249 Cases —

Result of Operation	No. Cases	Cond. before Operation				Present Condition				Remarks
		Bed	Amb.	Sputum	Pos. Neg.	Bed	Amb.	Wk.*	Sputum	
Technically and clinically successful..	152	120	32	146	6	8	18	126	152	Working 83%
Technically unsuccessful, clinically successful.....	19	19		19			7	12	19	Working 68%
Technically successful, clinically unsuccessful.....	2	2		2						Two dead: 1 from spontaneous px. after op. 1 from hemorrhage opposite lung
Technically and clinically unsuccessful	76	62	14	76						

{ This group comprised cases presenting adhesions unsuited for operation. In most cases minor adhesions of no technical importance were severed. All appropriate cases were subjected to other operative collapse procedures. The end result is not attributable to the pneumolysis—consequently not recorded here.

* Wk. = Working

technically and clinically successful. Of these, thirty-two cases had to deal only with string and cord adhesions. In eighty-five cases, band adhesions alone were present; in twenty-two cases, other operable types of adhesions were found.

The technically unsuccessful but clinically successful group comprises nineteen cases presenting all the above types of adhesions, as well as others described under the classification of "adhesions." This group embodied cases wherein some adhesions, because of their character, were left uncut, yet sufficient collapse of the lung was obtained to bring about a satisfactory clinical result.

It has been demonstrated that clinical success is not always dependent upon severance of all adhesions. A determination as to the ones of technical importance should be made and only these cut (see frontispiece). Of the 249 cases forming a basis of this study, one hundred and seventy-one (70 per cent.) obtained a clinically successful result.

The technically successful but clinically unsuccessful cases were two; one of these, previously quoted, died from a spontaneous pneumothorax seven days after operation, and the other of sudden profuse hemorrhage from the successfully collapsed lung (twenty-four hours after operation), which, due to her position with the pneumothorax side up, filled the dependent sound lung. This patient had profuse bleeding from an open cavity before operation; the purpose of the latter was to affect closure of the cavity. The technically and clinically unsuccessful group comprise seventy-six cases; forty of these presented only diffuse adhesions, and thirty-four had diffuse and fold adhesions in combination with others of the string, cord or band type. These latter were severed; but the remaining inoperable adhesions prevented a satisfactory collapse of the lung.

The remote results in the cases operated upon are shown in Table 3. Of the 152 technically and clinically successful ones, one hundred and twenty were bed cases and thirty-two were ambulant before operation; one hundred and forty-six cases had a positive sputum; in six, it was negative. All these latter six were cases who had been under satisfactory pneumothorax but the adhesions were contracting and causing an early lung expansion. These cases had been under observation over five years, during which time pneumothorax treatment was continued for at least two years. Eight more

recent ones are still bed cases; eighteen are ambulant and 126 are working—all have a negative sputum. Of the nineteen technically unsuccessful but clinically successful ones, all were bed cases and all had tubercle bacilli in their sputum. Four years after operation seven are ambulant and twelve are working. All have a negative sputum.

CONCLUSIONS

Owing to the great risk of disease invading the opposite lung, gastro-intestinal tract or larynx from an unclosed cavity, continuation of an unsatisfactory pneumothorax over a protracted interval is inexcusable. Our experience covering the past nine years, including approximately 950 cases of artificial pneumothorax, has disclosed that intrapleural pneumolysis under thoracoscopic guidance will convert approximately 70 per cent. of unsatisfactory cases of pneumothorax into satisfactory ones. We have shown that less than 15 per cent. of recoveries take place as the result of the continuation of an unsatisfactory pneumothorax, and that the use of high intrapleural pressures in an attempt to stretch adhesions is accompanied with utmost danger. If after a probation of three to five months, a satisfactory collapse of the lung is retarded by adhesions, it is quite safe to state that further continuance of the pneumothorax will probably not produce a satisfactory end-result. After a trial has been given, an unsatisfactory pneumothorax should be converted into a satisfactory one by intrapleural pneumolysis; other surgical collapse methods should be utilized if this is impractical.

PHRENIC NEURECTOMY

After having employed artificial pneumothorax and its adjunct, intrapleural pneumolysis, to the fullest extent, we are confronted with a group of cases, comprising approximately 35 per cent., wherein the above two procedures either cannot be utilized or are unsuccessful because the adhesions are not of a type appropriate for cutting. Without subjecting the patient to further trial of the usual sanatorium regimen, one should consider instead methods of putting the lung at rest through other collapse procedures.

We have for our next consideration phrenic neurectomy and thoracoplasty, and in a few selected cases extrapleural pneumolysis,

direct cavity drainage, or other methods referred to later. However, before contemplating the major methods, one should employ the minor one, namely, phrenic neurectomy. This operation was proposed by Stuertz in 1912—its purpose being to paralyze the hemidiaphragm and provide functional rest for the lung. Atrophy of the diaphragmatic musculature was followed by its gradual ascent into the hemithorax causing a reduction in the lung volume, variously estimated from one-fourth to one-third. Thus, the anatomical and physiological changes due to pneumothorax took place to a certain extent. Resection of a short piece of the phrenic nerve was proposed by Stuertz to prevent its regeneration; but numerous observers, including one of us (R.C.M.) and Marr Bisailon, reported in 1914 that the hemidiaphragm paralysis was often neither complete nor permanent. The operation gradually passed into disuse until the studies of Felix and those of Goetze showed that the simple resection of the phrenic nerve proposed by Stuertz was disappointing because in fully 25 to 35 per cent. of the cases the phrenic nerve, while taking its origin usually from the 4th. cervical and often from the 3rd. and 5th. roots (or all three) also receives additional fibers from the 6th., 7th., 8th. and sometimes the 1st. thoracic root. It was demonstrated very clearly that these accessory communications join the phrenic nerve below the site of resection proposed by Stuertz; consequently, the diaphragm continued to receive enervation in spite of the Stuertz simple resection.

The most common accessory communication from the cervical plexus to the phrenic nerve is from the 5th. cervical root,—either near or in combination with the nervus subclavius. In the latter case the accessory root departs from the nervus subclavius just before the latter enters the muscle of the same name. The accessory branch continues downward, usually in front of the subclavian vein to join the phrenic nerve just behind the sternal end of the 1st. rib.

Felix proposed an exaimesis of the phrenic nerve, after its section, by winding it around a Thearsch or hemostatic forceps in order to interrupt impulses coming from the accessory branches, as well as any communicating sympathetic fibers. However, complete evulsion of the nerve is unnecessary. One can be assured that complete interruption of the phrenic and associate fibers has taken place if 12 cm. of the nerve are evulsed. We have always seen a hemidiaphragm paralysis result when even 8 to 10 cm. have been removed.

Goetze overcame accessory impulses by resecting all accessory fibers between the phrenic and the cervical nerves. The Goetze operation, or radical phrenicotomy, is a much more time-consuming procedure than the phrenico-exaimesis of Felix, which is by far the most generally performed. At the same time the latter is not devoid of danger and complications, in view of the anatomical studies carried out by Plenck and one of us (R.C.M.): Plenck and Matson dissected out 112 phrenic nerves in cadavers. 72 per cent. were found typical,—that is, the phrenic nerve arose from either the 3rd., 4th. or 5th. cervical nerves, the fibers joined together from one main trunk and passed downward and inward across the anterior surface of the scalenus anticus and entered the thorax behind the subclavian vein. In 28 per cent. of cases the nerve was atypical; in twenty-three instances, accessory fibers came from the nervus subclavius; in six cases the accessory fibers came from the 5th. cervical near the origin of the nervus subclavius. In five instances the accessory phrenic looped around the subclavian vein before joining the phrenic nerve. This type is obviously a dangerous form for exaimesis because of the possibility of tearing the vein. Various other combinations were found, such as a double phrenic (eight times). In three instances the phrenic nerve was not found on the anterior surface of the scalenus anticus but lateralwards to the muscle. Once an accessory phrenic passed through the wall of the subclavian vein. In such a case, again, an exaimesis would probably be followed by fatal hemorrhage.

Based upon these anatomical studies, our surgical approach is through the subclavian triangle because of the accessibility to accessory fibers, which, if present, are sectioned and an exaimesis then performed.

TECHNIC

We make an incision 2 to 3 cm. long, 2 cm. above and parallel with the clavicle, extending from the posterior border of the sternomastoid lateralwards, and enter the subclavian triangle below the omohyoid (figure 4). The platysma, superficial and deep fascia are divided. The external jugular is either ligated and cut or retracted. The pyramidal fat body, together with the small lymph glands usually met with, are retracted. Below, one will see the transverse scapular artery, and above, the superficial cervical artery, both of

which cross the phrenic transversely in front of it. The phrenic is sought out on the anterior surface of the scalenus anticus, separated from the fascia and picked up with the tenaculum. After positive identification and further examination of the field for associate branches (for which purpose the incision may be lengthened), the nerve is injected with novocain and resected. If no complex types are encountered an exaeresis is done. On the other hand, should associate fibers be found, these are severed and then an exaeresis of the main stem performed. We feel that an exaeresis is perfectly safe under these conditions.

INDICATIONS

The indications for the operation are as follows:

1. As an independent procedure in (a) all cases wherein an artificial pneumothorax is indicated and wherein there has been a failure to introduce gas, or establish a satisfactory collapse because of the presence of pleuritic adhesions which cannot be severed by the closed method of intrapleural pneumolysis; (b) for social or economic reasons in cases wherein the patient is unable to undergo a prescribed course of pneumothorax therapy.

2. Before every thoracoplasty for the following reasons:

- a. The improvement following an induced hemidiaphragmatic paralysis may lead to recovery,—thus sparing the patient the necessity of a major surgical operation.

- b. In favorable cases the patient is rendered a far better surgical risk because of the marked improvement which follows a satisfactory hemidiaphragm paralysis.

- c. Not only is the sputum quantity reduced but the cough is facilitated,—thus lessening the danger of aspiration infection, should a thoracoplasty be resorted to.

- d. To effect as much collapse as possible through the rising diaphragm, thereby reducing the number and amount of ribs to be removed later.

- e. To permit the heart partial accommodation of itself to increased functional activity that a thoracoplasty will impose upon it later.

- f. As a test of the integrity of the contralateral lung.

According to some surgeons a phrenic neurectomy is of value

chiefly as a "test" operation before a thoracoplasty, in cases with suspicious changes in the better lung, particularly apical lesions. If the operation is followed by an increase of the physical or roentgenological findings, fever, or the patient's general condition becomes worse, an extrapleural thoracoplasty is absolutely contraindicated. On the other hand, if there is no reaction, one may justly proceed with the major operation.

A study of our material indicates that one cannot accept with blind faith the result of a phrenic neurectomy as a "test" operation, since we have seen a contralateral lung lesion withstand the "test" operation but exhibit activity after a thoracoplasty. We have also observed an essentially negative contralateral lung exhibit disease following the "test" operation but pass through a complete thoracoplasty undamaged, although the diseased area in the contralateral lung was essentially the same before each procedure.

3. Supplementary to artificial pneumothorax where non-operable adhesions are preventing a satisfactory lung collapse—to provide additional collapse.

4. Threatened early obliterative pneumothorax combined with oleothorax to maintain collapse.

5. When one has to deal, towards the end of a course of pneumothorax therapy, with an originally very extensively diseased lung, in order to diminish the capacity of the hemithorax to accommodate a lung which has been shrunk by scar tissue changes—thus lessening the danger of (a) reexpansion of excavated areas, (b) secondary bronchiectasis, (c) retraction of heart and mediastinal contents.

6. In the treatment of empyema as a complication of pneumothorax for the purpose of lessening the area of pyogenic membrane.

COMPLICATIONS

While phrenic neurectomy is a minor operation, it is not without danger and should not be attempted by anyone not possessing a thorough knowledge of the topographical anatomy of the neck, and particularly a knowledge of the anomalies of the phrenic nerve.

The most serious complications to be contended with are damage to vascular structures, important nerve structures, and, relatively unimportant, the thoracic duct. Damage to blood-vessels has resulted in fatal hemorrhage or death from air embolism; also wounding the

thyrocervical trunk, which has occurred in the hands of even competent surgeons, has necessitated ligature of the subclavian artery.

Instances have been reported where the sympathetic trunk, also the vagus nerve, was damaged. Sauerbruch has seen several cases, operated outside his clinic, wherein the vagus; sympathetic and long thoracic nerves were erroneously cut instead of the phrenic.

In our series of approximately 500 operations we have encountered no serious complications.

After a complete interruption of nerve impulse to the hemidiaphragm has been effected, and if adhesions or thickening of the diaphragmatic pleura do not prevent, the diaphragm immediately assumes the expiratory position, and under the fluoroscope it is motionless on quiet breathing. On deep inspiration it will rise slightly into the chest cavity as a result of the higher abdominal and lesser intrapleural pressure.

The most sensitive and easily applied test of a hemidiaphragmatic paralysis is the so-called "sniffing test" (Hitzenberger phenomenon), elicited by directing the patient to "sniffle." The paralyzed hemidiaphragm rises into the chest, whereas, it descends on the other side.

While the paralyzed hemidiaphragm, if not hindered, assumes the expiratory position immediately after operation, it continues to rise gradually throughout the ensuing months as muscle degeneration and atrophy progress. This is still further accentuated by the shrinkage of scar tissue as healing in the lung progresses. The maximum rise may not be attained for a period of from six months to a year or more, and its amount may be from 9 to 13 cm.

The results of an induced hemidiaphragm paralysis are more dependent upon the rise of the diaphragm and the degree of collapse of diseased lung tissue effected thereby than upon merely placing the diaphragm at rest.

RESULTS

Space does not permit an analysis of our entire series; however, the value of the operation can be shown in the following classes of cases. In those types of tuberculosis wherein a pneumothorax is impossible and a thoracoplasty is contraindicated, the value of an induced hemidiaphragmatic paralysis is unquestioned, according to our own experience. For instance, in one group of thirty-four cases of the productive type of tuberculosis, predominantly unilateral,

where a thoracoplasty was contraindicated because of the presence of active or progressive disease in the contralateral lung, we have obtained most gratifying results: 52 per cent. were much improved and 38 per cent. were improved; in 44 per cent., the sputum became negative to the tubercle bacillus, and in the 52 per cent. rated as "much improved," the improvement was so marked that a thoracoplasty became unnecessary. (All of these patients made clinical recoveries.)

In another group of thirty-two cases of essentially unilateral pulmonary tuberculosis, wherein a pneumothorax was impossible and a thoracoplasty was indicated, we have observed almost equally pleasing results: 35 per cent. of these patients were much improved, and 28 per cent. were improved. All patients rated as "much improved" are capable of making a clinical recovery. In 40 per cent. of the above cases, the sputum became negative to the tubercle bacillus. In 35 per cent. of these cases, the patient so improved that a thoracoplasty became unnecessary.

EXTRAPLEURAL THORACOPLASTY

Next to a satisfactory pneumothorax, an extrapleural thoracoplasty is the most valuable method of collapsing the lung and putting it at rest. It should not be considered however until pneumothorax has been attempted and adhesions prevent either the introduction of gas or an insufficient quantity to establish a satisfactory pneumothorax,—provided also that the adhesions are not of a suitable type for operation. Furthermore, a thoracoplasty should not be resorted to until a phrenic neurectomy has been done and a reasonable time has elapsed to study the result (three to six months), unless it is obvious that the diaphragm is so bound down by adhesions that no rise is to be expected.

Paravertebral extrapleural thoracoplasty should be done in two or more stages, depending upon the condition of the patient. It is very essential that the posterior ends of the ribs be removed close up to the transverse process of the vertebra to assure a good chest wall collapse. It has been our custom to resect portions of the upper five ribs first, then proceed with a resection of the lower five or six, depending upon the case. If a large cavity is present in the upper lobe, we follow the upper phase operation with a resection of the upper four or five ribs close to the sternum, through a mid-axillary line

incision, and then proceed with a lower phase. If the case presents predominantly lower lobe pathology, we do the lower phase first, which is followed by the upper phase. A partial thoracoplasty, whether unilateral or bilateral, may be considered in certain carefully selected cases where the lesions are apical or subapical, with essential freedom of disease below the 4th. or 5th. rib posteriorly.

The selection of cases for thoracoplasty requires stricter study than for a pneumothorax. Exudative forms of pulmonary tuberculosis should not be subjected to the operation, as their improvement is not advanced by it. Thoracoplasty is indicated in pulmonary tuberculosis, with or without cavity formation, when the disease is unilateral and of a productive or fibroid type, provided the patient is in fairly good general condition and not too old. If large cavities are present, the outlook is less favorable. According to our experience the combination of a large open cavity with a pneumothorax of long duration gives a less favorable prognosis than the same type of case without a pneumothorax.

Rapidly advancing forms of tuberculosis should not be subjected to thoracoplasty. And while it is not essential that the contralateral lung be entirely free of disease, nevertheless, a contralateral lung lesion must be arrested and not too extensive.

The contraindications for thoracoplasty, in addition to those which obtain for pneumothorax, should include poor surgical risks.

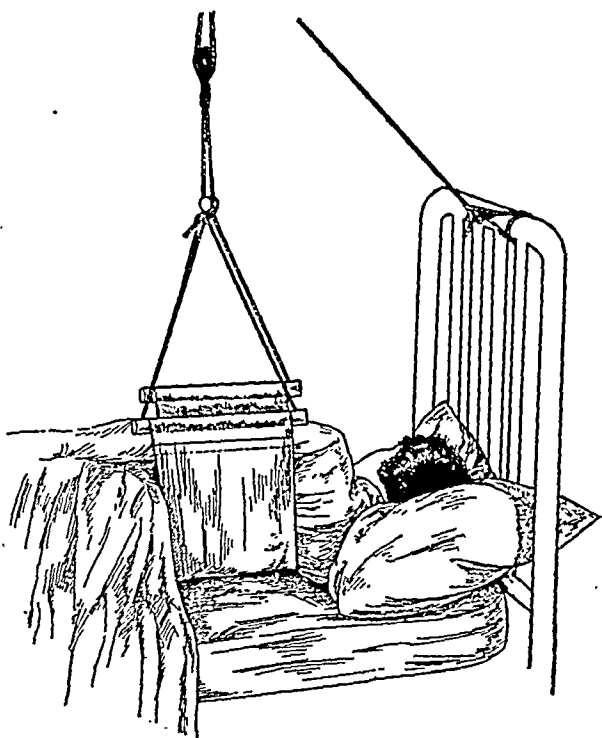
Our preoperative preparation consists in complete laboratory studies—blood transfusions are given, if indicated. During the week prior to operation the patient is placed on a proteid-free, carbohydrate-rich diet with abundant water and at times, hard sugar candy after meals,—also, the patient is trained in early morning cavity drainage, and prepared psychically for operation. The day before operation he is placed in an oxygen tent one-half hour out of every three hours. This procedure is continued after operation. We feel it has contributed materially to our low postoperative mortality.

We prefer to do the operation under local anesthesia combined with light ethylene. In good risk cases, with normal blood pressure, we often use sodium amytal in hypnotic doses, followed by ethylene gas. For preoperative medication we resort to nembutal, ortal sodium or pantappon. During the operation it is essential that the blood pressure be constantly checked and the operation concluded

the moment any manifestations of shock appear. We are happy to say, as will be noted later, that we have never had a postoperative death from shock. In multiple phase operations the stages should follow one another promptly within the course of one or two weeks.

The postoperative care is extremely important and should be in the hands of nurses who have had special training in this type of surgery. As soon as possible after the paravertebral operation has

FIG. 4



Thoracic Hammock for Increasing Chest Wall Collapse and Preventing Scoliosis.

been completed, the patient is placed several hours daily in a thoracic hammock, designed by one of us (R.C.M.) (Figure 4). This almost entirely prevents any deformity. During the period of osteogenesis the chest is kept tightly strapped with adhesive plaster.

COMPLICATIONS

We have experienced no deaths from postoperative shock, hemorrhage or wound infection in our entire series of 310 operations on

130 cases. We have had two postoperative deaths within one week after operation—both cases resulted from cardiac failure. The remaining deaths were due to the development of disease in the contralateral lung or its activation, or to progressive disease in the intestines.

RESULTS

The results of a well-executed thoracoplasty are striking. Clinical improvement follows shortly after the postoperative effects have passed. The results show about the same percentage of recovery as noted with a satisfactory pneumothorax. (Table 4)

TABLE 4
End Results of Thoracoplasty

		Per cent.	
Number of cases.....	130		
Number of operations.....	310		
Dead—Directly due to operation.....	2	1.53	—Direct Operative Mortality
Dead—Indirectly due to operation (none from wound sepsis).....	12	9.23	} —Indirect Operative Mortality
Dead—From causes not due to operation.....	14	10.78	
			—Total Dead—21%
Worse—(Aspiration pneumonia) recent cases...	2	1.53	
Unchanged—(Recent cases, more collapse necessary).....	8	6.15	
Somewhat improved—(Recent cases).....	6	4.61	
Greatly Improved—Ambulant, recovery probable	26	20	Greatly Improved —and Well Group— 66.1%
Clinically Well—(All symptoms and positive sputum absent for two years under ordinary conditions of life).....	60	46.15	

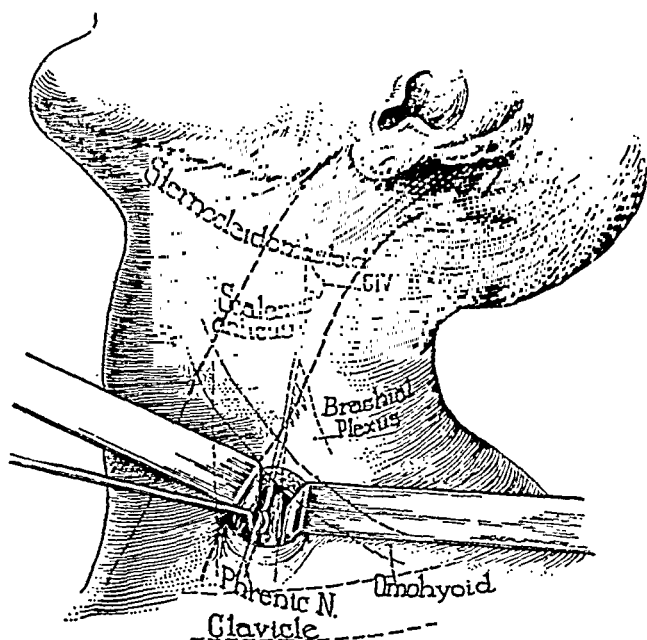
OLEOTHORAX*

The term "oleothorax" was proposed by Bernou in 1922 to indicate the use of massive quantities of an antiseptic oil in the pleural

* A full discussion of oleothorax therapy, particularly detailed instructions regarding technic, is not possible within the scope of this paper. For such information the reader is referred to an article by one of us (R. W. M.) in the *American Review of Tuberculosis*, 25:419, 1932.

cavity for therapeutic purposes. This method of treatment has received its greatest popularity in Europe, particularly France, where it originated and from where a tremendous amount of literature has emanated. Oleothorax therapy has as yet received little attention in America. Like all new methods of treatment it has been bitterly assailed by those disappointed in the end results, but by others who have had perhaps more experience or a better understanding of its use, it has been strongly supported, and by them the failures of those

FIG. 5



Authors' Surgical Approach to the Phrenic Nerve.

who condemn it have been attributed to a lack of judgment in the selection of material, the failure to recognize proper indications for its use, improper technic in its application, or inadequate observation of cases under treatment.

In the light of our present knowledge oleothorax therapy is indicated under the following conditions:

1. As a *Disinfection oleothorax* in certain types of pneumothorax empyemata.
2. As an *Inhibition oleothorax* (*oleothorax antisymphysaire*).

3. As a *Compression oleothorax*.
4. For the purpose of stiffening a labile mediastinum.

Contraindications for the use of an oleothorax are: (1) pleuropulmonary fistula with large opening, (2) ordinary serofibrinous exudate complicating an artificial pneumothorax, (3) ordinary pneumothorax empyema (which is tolerable, non-toxic and *does not tend to chronicity*), (4) as a substitute for a pneumothorax in patients who, for various reasons, are unable to undergo the prescribed course of pneumothorax therapy.

An oleothorax is contraindicated in the treatment of pleuropulmonary fistula with a large opening for the reason that the oil leaking through the fistulous tract not only adds to the discomfort of the patient by the continuous expectoration of oil, but there is also the added danger of an aspiration infection into healthy lung tissue, or even suffocation.

Oleothorax therapy is contraindicated in the treatment of an ordinary serofibrinous exudate, or a tolerable non-toxic empyema which does not tend to chronicity, because the oil is likely to prove irritating to an already inflamed pleura, which responds with the formation of a purulent exudate or aggravation of a purulent exudate already present.

An oleothorax should be resorted to in the presence of a serofibrinous exudate, or a purulent exudate which is well-borne, only when this complication tends to chronicity, is not relieved by repeated aspiration, and is associated with a chronic, productive pleuritis which tends to early obliteration of the pneumothorax cavity.

Oleothorax is contraindicated as a substitute for pneumothorax therapy in patients who, for one reason or another, are unable to undergo the prescribed course of pneumothorax treatment, for the reason that the oleothorax patient requires much more careful observation than is required in pneumothorax therapy. Consequently, if the patient is unable to submit to the former, he is an undesirable candidate for the latter because of the danger of complications.

SELECTION OF OIL

As a base, two types of oil are used—mineral and vegetable; the first in the form of paraffin oil and the second in the form of olive or

Wesson oil. The oil is rendered antiseptic by the addition of gomenol in a strength varying from 1 to 10 per cent., depending upon the purpose for which it is employed. For the purpose of a disinfection oleothorax, gomenolized vegetable or mineral oil is used in a strength of from 1 to 10 per cent. When an oleothorax is established for the purpose of inhibiting expansion of the lung, or as a compression oleothorax, pure paraffin oil, or paraffin oil to which 1 per cent. gomenol has been added, is employed.

Preparation of oil.—In preparing the oil it is customary to add the gomenol in the desired strength, to the vegetable or paraffin oil, then allow the mixture to stand for three weeks so that the two oils become thoroughly mixed. This mixture is placed in flasks, stoppered with a small pledget of gauze or non-absorbable cotton, which is covered with rubber tissue. The flasks are then placed in an autoclave and sterilized by subjecting them to thirty pounds of steam pressure for twenty minutes.

Disinfection oleothorax.—The fundamental principle of disinfection oleothorax is that the pleural cavity should be completely drained of its purulent exudate by aspiration and *replaced with an equal quantity of the oil mixture*. After aspiration of the purulent exudate it is occasionally desirable to irrigate the pleural cavity with saline solution before injecting the oil mixture.

Pneumothorax empyemata are classified, for therapeutic purposes, into the non-toxic, or tolerable, and the so-called toxic, or virulent, types. The latter are usually due to a mixed infection. A disinfection oleothorax is employed for the relief of a non-toxic pneumothorax empyema when the condition tends to chronicity and does not respond to frequent aspiration. Since these exudates are usually tuberculous in nature, gomenolized paraffin oil in a strength of 1 to 5 per cent. is employed. The toxic or virulent type of pneumothorax empyema is characterized by profound constitutional disturbance. The exudate is usually due to a mixed infection. For the treatment of this condition gomenolized paraffin, olive or Wesson oil is employed in a strength of from 5 to 10 per cent., since it has been shown that gomenol in weaker solutions is unable to destroy or inhibit the growth of mixed infection organisms.

In the treatment of the non-toxic type of pneumothorax empyema,

simple aspiration and oil replacement usually suffices to bring about relief.

In the toxic type of empyema much more drastic measures must be resorted to and the best results will be obtained by a thorough irrigation of the empyema cavity with saline solution following aspiration of its purulent contents, before making the oil injection. The aspiration of exudate and oil replacement is usually followed by a subsidence of fever, but the treatment should be repeated immediately the fever begins to recur.

In the non-toxic type of pneumothorax empyema the aspiration of exudate and oil replacement is usually necessary at intervals of a week, in the beginning of the treatment, and after a few aspirations and oil replacements, the interval may be extended to a month or six weeks.

In the toxic type of pneumothorax empyema the aspiration of exudate, irrigation of the pleural cavity and oil injection is frequently necessary at intervals of every two or three days in the beginning of the treatment, but once the toxicity of the process subsides and the patient becomes afebrile, irrigation of the empyema cavity after aspiration is no longer necessary and the case is handled as a non-toxic type of pneumothorax empyema.

One should never establish a complete oil blockade of the pleural cavity in a disinfection oleothorax for the reason that the reaccumulation of exudate is likely to so elevate the intrapleural pressure that a lung perforation results.

Inhibition oleothorax (*oleothorax antisymphysaire*) is employed to prevent expansion of the lung in threatened early obliterative pneumothorax wherein a satisfactory collapse cannot be maintained by air inflations, even though the inflation intervals have been shortened and the pressure has been increased.

A *compression oleothorax* is employed to reestablish collapse in cases wherein air inflations properly carried out have failed to maintain a satisfactory collapse of the diseased lung tissue.

If the oleothorax provides collapse to the diseased lung tissue only, it is termed an "elective oleothorax."

In the above types of oleothorax a complete oil blockade of the pleural cavity is established.

Labile mediastinum.—Air inflated into the pleural cavity natu-

rally exerts its greatest influence at the point of least resistance. Since adhesions almost invariably exist, at least to some extent, between the diseased lung tissue and the chest wall, and offer more or less resistance, a labile mediastinum being the point of least resistance responds to air inflations by bulging before a satisfactory collapse of the diseased lung tissue can be accomplished. Adhesions of this type should be severed by means of an intrapleural pneumolysis. If this is impossible one should endeavor to stiffen the labile mediastinum, after which an attempt may be made to stretch the offending adhesions by means of higher air pressure.

If, in a case of an unsatisfactory pneumothorax with a labile mediastinum, it has been decided to abandon the pneumothorax and resort to a thoracoplastic collapse, then the labile mediastinum should be stiffened before subjecting the patient to operation in order to prevent a postoperative "mediastinal flutter" which might prove serious, if not actually fatal.

Thickening or stiffening of a labile mediastinum is brought about by inducing slight pleural reactions which are localized to the bulging area. With this end in view the patient is placed recumbent in the dorsolateral position upon the healthier side and the injection needle so introduced, in the 2nd. or 3rd. intercostal space close to the sternum, that it barely penetrates the pneumothorax cavity. From 5 to 10 cc. of 1 per cent. gomenolized oil are then slowly injected and permitted to flow down the anterior chest wall into the bulging mediastinum. The patient should remain in this position for from one to two hours in order to permit a localized action of the oil, after which the patient is seated upright and a 13 gauge needle is inserted into the lowermost portion of the pneumothorax cavity. The oil is then aspirated and the lower portion of the pneumothorax cavity irrigated with saline solution. These injections should be repeated from time to time until stiffening of the mediastinum has taken place.

Testing the sensitiveness of the pleura.—Before attempting to establish a complete blockade of the pleural cavity it is extremely important to test the sensitiveness of the pleura to oil, especially if one has to deal with a so-called "virgin pleura,"—that is, a pleura which has not been the site of a former or recent inflammatory process.

Since the pleura is not so sensitive in the presence of a purulent exudate a preliminary test is not necessary before instituting a disinfection oleothorax.

In pneumothorax therapy failure to maintain a satisfactory collapse of diseased lung tissue for a period of time sufficient to insure recovery is usually due to an "early obliterative pneumothorax," which is readily recognizable roentgenologically; clinical manifestations are evidenced by the rapidly rising intrapleural pressures. Once it has been decided that a satisfactory collapse can no longer be maintained by air inflations a test of the sensitiveness of the pleura to oil should be made, with the idea of converting the pneumothorax into an oleothorax.

A test of the sensitiveness of the pleura is made by injecting 2 cc. of 1 per cent. gomenolized paraffin oil, or pure paraffin oil, into the pneumothorax cavity. If no reaction occurs, a second test dose of 5 cc. is made at the end of a week or ten days. If no reaction occurs, the test doses are doubled at each sitting and the injections are repeated at intervals of a week or ten days until one is satisfied that the pleura is not sensitive to the oil. After having attained a dose of 75 to 100 cc. of oil without reaction, further injections are made at the time of the regular air inflation interval. The dose of oil is increased 100 cc. at each sitting until a complete oil blockade has been established. One should not however exceed a dose of 400 to 500 cc. in the adult male, or 300 to 400 cc. in the female at one sitting. An oil blockade slowly established in this manner is much less likely to be associated with complications.

Before attempting to establish a compression oleothorax the pleural cavity should be prepared for the high oil pressures by means of preliminary high air pressures,—otherwise, there is great danger of inducing a pleural reaction or bringing about a lung perforation.

REACTIONS

Reactions to oil, like air, are likely to occur at any phase of the treatment. In some cases no reaction will be observed until a dose of oil amounting to 50 cc. or more has been injected. The reactions are intrapleural and constitutional in nature. The intrapleural reaction is manifested by pain over the corresponding hemithorax and

by the formation of an exudate which may appear within forty-eight hours after the oil injection, or at the end of a week or ten days.

If the pleural reaction is mild the exudate formation is usually serofibrinous and not associated with constitutional symptoms. If the oil injection proves very irritating to the pleura, the exudate formation appears shortly and, while serofibrinous at first, it usually becomes rapidly purulent. An exudate of this type is usually associated with marked constitutional phenomena: high fever, severe pain, prostration, anorexia, etc.

In some cases the reaction is entirely constitutional in character. If mild, the patient complains only of a slight elevation of temperature, malaise, etc. But if the constitutional reaction is severe, the patient complains of chills, high fever, extreme prostration, nausea, vomiting, etc. Reactions of this type are almost invariably followed by an exudate formation which is usually purulent in character.

Oil replacement.—Since every type of oil is absorbable to some extent, and this depends largely upon the permeability or absorptive capacity of the pleura, as well as the type of oil used, oil replacements are necessary from time to time in order to maintain a proper collapse.

Before making an oil replacement it is exceedingly important to determine the presence or absence of an exudate. This is easily done by inserting an aspiration needle at the lowermost portion of the oleothorax cavity, after which the patient is seated upright and the contents of the pleural cavity drawn into a syringe. If pure, clear oil is recovered the patient is placed recumbent in the dorsolateral position, after which the injection of oil is made. There can be no fixed rule regarding the quantity of oil necessary for replacement purposes. If the oil blockade has been used for the purpose of inhibiting expansion of the lung the oleothorax should be maintained at a neutral pressure. Consequently, in making oil replacements one should cease the injection immediately upon encountering resistance in pressing the syringe piston. If a compression oleothorax is being maintained the pleural cavity should be kept well "stretched," but this must be done slowly and in a cautious manner, after having tested the integrity of the pleura by means of preliminary high air pressures. The pressure under which the compression oleothorax

exists can be approximately determined by the use of an oil manometer.

If, at the time of making the oil replacement, an exudate is encountered, it should be withdrawn and further oil injections withheld until the exudate formation has entirely ceased. Cases tending to exudate formation should be observed carefully lest the exudate formation so elevate the intrapleural pressure that a lung perforation takes place. If the exudate formation tends to persist and form in considerable quantities, it may be necessary to abandon the oil blockade by aspirating all oil. Later, if the irritability of the pleura subsides, another attempt should be made to establish an oil blockade.

After an oil blockade has been established for a year or more, oil replacements, if made at all, are made at rare intervals—but one should occasionally explore the oleothorax cavity in order to determine the pressure under which the oleothorax exists, and to make sure that an exudate does not exist. If a negative pressure is found further replacements are necessary.

Withdrawal of the oleothorax.—After an oleothorax has served its purpose and a clinical recovery has apparently taken place, the oil should be withdrawn in small quantities at regular intervals over a period of time sufficient to convince one that the lung lesion remains healed. From six months to a year or more should be occupied in the withdrawal process—thus permitting a gradual reexpansion of the collapsed lung.

Late complications.—In oleothorax therapy, as in pneumothorax therapy, the pleura is likely to become irritable at any phase of the treatment and respond to air inflation or oil injection with an exudate formation. And in some cases, wherein an oil blockade has been established and remained undisturbed for from one to many years, the oil may suddenly act as a foreign body, producing an inflammatory reaction associated with exudate formation. This exudate formation may be manifested only by a gradual elevation of the temperature, without any symptoms referable to the oleothorax. At other times the patient complains of having a so-called “mild attack of Grippe.” In still other cases the patient becomes suddenly acutely ill with chills followed by a high fever associated with great prostration, nausea and occasionally vomiting. Once an oil blockade has been established, the occurrence of an unaccountable fever, or

any unexplainable symptom complex, demands investigation of the oleothorax cavity. A good radiograph may show two fluid levels, and if such a finding is present, one may feel assured that the lower, denser shadow is due to a purulent exudate. The pleural cavity should next be explored and a specimen of its contents aspirated into a syringe. Frequently, one's efforts will be rewarded by the recovery of a small quantity of purulent exudate, in which event the exudate as well as some of the oil should be aspirated. This treatment should be repeated from time to time, depending upon the rapidity of the formation of the exudate and the character of the patient's temperature. If the exudate formation tends to persist, or the elevation of temperature does not subside, the oleothorax should be abandoned by withdrawing all oil, after which the empyema should be treated by means of aspiration and irrigation.

END RESULTS

Satisfactory results can be expected in approximately 60 per cent. of the cases wherein the oleothorax has been employed for disinfection purposes,—that is, the empyema clears up and the collapse can be maintained either by air inflations or a complete oil blockade.

When an oleothorax is employed to inhibit expansion, satisfactory results can be expected in approximately 50 per cent. of the cases. By far the best results will be achieved in the "elective" oleothorax cases, and the most unsatisfactory results will be obtained in cases wherein the oleothorax has been established for compression purposes.

EXTRAPLEURAL PNEUMOLYSIS

In the presence of circumscribed apical cavities, either unilateral or bilateral, one may in certain very selected cases consider extrapleural pneumolysis. However, the case should be one wherein a pneumothorax has been attempted or failed because of diffuse and inoperable adhesions by the intrapleural method, and a phrenic neurectomy has been performed without success.

Extrapleural pneumolysis has for its objective selective collapse of the involved portion of the lung. This is accomplished by exposing the parietal pleura through an intercostal incision, if there is

sufficient space between the ribs to introduce a finger,—otherwise, a short section of one or two ribs is removed, after which the parietal pleura is stripped from the endothoracic fascia, producing a pocket which is filled with a flap of muscle, fat or paraffin, with neutral bismuth subcarbonate and 1.5 per cent. vioform. Or one may pack the space with a rubber dam and fill with gauze. Of the various filling materials, one may say that the fat and muscle fill are the least satisfactory. The paraffin bismuth paste fill is not infrequently followed by ulceration of the pleura and discharge of the paste into the lung cavity; it has generally been unsatisfactory unless only a small fill is required. The authors have experienced a few successes with the rubber dam and gauze pack advocated by Lilienthal. A disadvantage of the latter method is that healing proceeds from the bottom of the wound and often leaves an unbecoming scar. In short, extrapleural pneumolysis is only of limited value. The operation is executed under local anesthesia. The site for the fill may be paravertebral, if the cavity is posteriorly located, or beneath the clavicle, if anterior. The method should be restricted to cavernous disease in the lung apex, with essential freedom of disease in the rest of the lung. Extrapleural pneumolysis is often indicated in cases wherein residual cavities have remained open following thoracoplasty.

MULTIPLE INTERCOSTAL NEURECTOMY

This operation, proposed by John Alexander, consists in the resection of the intercostal nerves of the diseased hemithorax. The nerves are exposed through a paravertebral incision under local anesthesia. The operation alone provides for mobilization of the hemithorax, and combined with a phrenic neurectomy may be of value in selected cases. The indications for multiple intercostal neurectomy are not so well defined as for the other operative collapse procedures. However, the disease should be predominantly unilateral. Disease in the contralateral lung, if present, should be quiescent. Exudative lesions offer less likelihood of benefit than productive ones. Intercostal neurectomy should not be considered unless artificial pneumothorax and phrenic neurectomy, or both, have been tried and failed. Little benefit can be expected from the operation in the presence of large cavities.

PNEUMONOTOMY

This operation, proposed by Lilienthal, consists in the opening and direct drainage of tuberculous cavities through the chest wall. Lilienthal has reported three successful cases, and we have one case in which a satisfactory result was obtained. The operation has many generally unrecognized possibilities.

THE VALUE OF COLLAPSE THERAPY IN THE HABILITATION OF THE TUBERCULOUS

The number of cases of pulmonary tuberculosis that should be treated by collapse therapy are still much less than would indicate its full utilization. Intrapleural pneumolysis is the most neglected procedure. It is unfortunate that the technic and its value is not more generally known. Many cases presenting adhesions are condemned to a thoracoplasty when the simpler operation, intrapleural pneumolysis, would give a satisfactory end result in approximately 70 per cent. of cases; and, in the end, the patient has a functioning lung instead of a permanently collapsed one.

Artificial pneumothorax will restore to health about 40 to 50 per cent. of all cases subjected to this treatment. Pleuritic adhesions will prevent a satisfactory collapse in about 40 per cent. of cases, but of these a large number will be appropriate for intrapleural pneumolysis, and 60 to 70 per cent. will be provided with a satisfactory pneumothorax.

More than half of the cases selected for collapse therapy will be successfully treated by artificial pneumothorax and its adjunct intrapleural pneumolysis. Of the remaining minority, where no gas can be introduced, or the adhesions are not suitable for cutting, a phrenic neurectomy will be indicated in most of them and upwards of 15 per cent. will recover.

A thoracoplasty will be indicated in about one-fifth of the cases selected for pneumothorax when the latter procedure cannot be carried out. Of these, 50 to 60 per cent. will recover.

If operative collapse therapy were utilized to the extent it is indicated we feel very certain that many thousands of otherwise hopeless cases of pulmonary tuberculosis would be restored to health and useful lives.

This contribution is based upon studies and material from the combined service of ourselves and associate, Dr. Marr Bisailon.

REFERENCES

- ¹ MATSON, RALPH C.: "Severing Adhesions in Artificial Pneumothorax by the Electrosurgical Method," *Surg., Gynec.& Obst.*, 58:619, 1934.
- ² MATSON, RALPH C.: "Operative Collapse Therapy in the Treatment of Pulmonary Tuberculosis," *West.J.Surg.*, 38:662, 743, 1930; 39:13, 1931.
- ³ MATSON, RALPH C.: "The Electrosurgical Method of Closed Intrapleural Pneumolysis in Artificial Pneumothorax," *Arch.Surg.*, 19:1175, 1929.
- ⁴ MATSON, RALPH C.: "Cauterization of Adhesions in Artificial Pneumothorax by the Jacobaeus-Unverricht Method of Closed Pneumolysis; Observations on 100 Cases," *Am.Rev.Tuberc.*, 19:233-305, 1929.
- ⁵ MATSON, RAY W.: "Exairesis of the Phrenic Nerve in the Treatment of Pulmonary Tuberculosis," *The American Review of Tuberculosis*, 22:1, 1930.
- ⁶ MATSON, RAY W.: "Oleothorax," *The American Review of Tuberculosis*, 25:419, 1932.

INDICATIONS FOR SURGICAL TREATMENT OF PEPTIC ULCER; METHODS; POSTOPERATIVE COMPLIC- ATIONS AND SEQUELAE AND THEIR TREATMENT

By I. W. HELD, M.D.

Attending Physician, Beth Israel Hospital, New York

and A. ALLEN GOLDBLOOM, M.D.

Adjunct Physician, Beth Israel Hospital, New York

ALTHOUGH the procedure to be followed when operation for peptic ulcer is decided upon is entirely within the domain of the surgeon, the indications for surgical intervention belong as well to the sphere of the internist. The ulcer patient consults the internist long—often years—before the condition progresses to the point where surgery is considered. Therefore, he must make the first decision regarding operation.

Fortunately, it is the prevailing opinion that surgical intervention for uncomplicated peptic ulcer should be contemplated only after thorough medical treatment has proved ineffectual. But it is as important for the internist not to delay surgical treatment too long, as it is to avoid recommending it too soon. We believe it is the internist's duty, also, to be clearly informed of the reasons for the various operative procedures. For example, he must know in what way operation is to remove the cause and restore normal function, and also the immediate and remote consequences and sequelae that may follow the different types of surgical procedure. It is only by being so instructed that he can give the best service to the patient in the way of preventing complications and sequelae, or in their treatment through dietetic and other medical methods. In general, the surgical indications for peptic ulcer may be divided into two groups: (1) Absolute, and (2) Relative.

ABSOLUTE INDICATIONS FOR OPERATION

1. *Perforation.*—It is almost self-evident that perforation indicates operation. Nevertheless, there exists a difference of opinion

as to the degree of perforation which makes operation necessary. It is quite true that pin-point perforations—particularly on the posterior wall of the stomach or duodenum—frequently heal by connective tissue formation and that the patient thereafter remains comfortable throughout the remainder of his life. One must realize, however, that it is difficult to judge, from symptoms alone, the degree of perforation. Occasionally an extensive perforation will not cause as severe, immediate symptoms as a very small perforation. Hence even though the perforation may be only suspected, we believe the patient should be given the benefit of the doubt and be immediately operated upon.

As a rule, the operation is a life-saving procedure, and the surgeon is eager to close the abdomen as quickly as possible. Generally he contents himself with stitching up the ulcer, or, if the ulcer is in the duodenum, with performing a gastroenterostomy. Remarkably enough, although the operation is only a palliative one, many patients have no further symptoms. There is no adequate explanation for this, although a possible reason may lie in the fact that many perforating ulcers give rise to no symptoms before perforation. It seems plausible to assume that an ulcer which did not give rise to sensory symptoms before operation will not do so afterward, during the process of repair. One is not to be misguided by the claim of certain authors that ulcers which perforate without first having given rise to symptoms must be present in hyposensitive individuals. Had the individual experienced sensory or secretory disturbances prior to perforation, he would certainly have been aware of them. Having had no such disturbances, naturally he complained of no symptoms. Likewise, the patient who suffers before perforation is very apt to continue after the operation to have symptoms which necessitate medical treatment or even a second, radical operation.

We take this stand regarding the indications for surgery in perforated ulcer because recovery depends entirely upon how soon after perforation the patient is operated upon. If operated upon within the first twelve hours, recovery takes place in 90 per cent. of cases. If surgery is delayed for from twelve to forty-eight hours, recovery occurs in 50 per cent. of cases; after forty-eight hours, the delay is almost always fatal. Therefore, we are of the opinion that it is

better to have the surgeon operate and find a very small or no perforation than to wait and find general peritonitis.

2. *Hematemesis*.—When hematemesis is repeated more than twice operation is unquestionably indicated. The only decision to be made is whether to wait for the bleeding to stop or to proceed at once. Fortunately, in the vast majority of cases, the hemorrhage subsides completely within two or three days so that one can wait for the patient to recuperate before the operation is performed. In some cases, however, despite all treatment, bleeding continues and the patient rapidly sinks. This is especially true if a pancreaticoduodenal vessel has ruptured. If bleeding is still profuse after twenty-four to forty-eight hours and there are continued manifestations of collapse, despite the use of blood transfusions and other methods of treatment, the surgeon should intervene without delay.

The responsibility for prompt treatment is great in bleeding cases because the patient may have had no ulcer symptoms whatever prior to the hemorrhage, which usually comes on unexpectedly. It has been our experience that when a patient bleeds more than twice he will bleed again and again. A case exemplifying both of these points is this. A patient came into the office with no symptoms, other than a feeling of weakness. While on the table, during the examination, he turned deathly pale, his blood pressure fell, and he was in collapse from profuse hemorrhage. He was transferred to a hospital at once and, after a few weeks, made a complete recovery. He had had absolutely no ulcer symptoms, although after the first hemorrhage roentgen ray examination showed a duodenal ulcer. This occurred in the spring of 1927. A year and a half later he again had a fainting spell and black stools, bleeding actively for several days. Following transfusions and medical treatment he recovered. We advised operation, but this was refused. However, after a poor response to medical treatment following a fourth hemorrhage he finally consented. A partial gastrectomy was performed. Since then the patient has been well. Throughout the period prior to operation, the patient had had no ulcer symptoms. It was, in fact, his introspection which saved his life because, after the second hemorrhage, he became so alarmed that, even against our advice, he insisted upon bringing his stool to the office daily for examination. On the evening before operation he felt entirely well. Slight ab-

dominal discomfort and a black stool, however, led him to seek aid at once so that it was possible to bring him into the hospital very soon after the hemorrhage began.

3. *Anemia due to slow oozing.*—Although anemia due to slow oozing is exceptional, when it does occur it can not only prevent healing of the ulcer, but, as is claimed by Boas, may lead to acidity and become the forerunner of cancer on the basis of ulcer. Surgical intervention, therefore, should not be delayed. When a patient bleeds or oozes slowly from a mucous membrane, the development of anemia is rapid and recovery is unlikely unless there is radical treatment, in contradistinction to the rather rapid recovery from anemia caused by bleeding from endothelial surfaces. We believe¹ that bleeding from an endothelial surface stimulates the hematopoietic system to the formation of new red blood cells much more rapidly than does oozing from a mucous membrane. It is well known clinically that when an acute hemorrhage from the lungs occurs, the patient does not develop anemia as rapidly as when bleeding comes from the stomach, uterus or rectum.

4. *Persistence of frequently recurrent ulcer symptoms.*—Should ulcer symptoms persist, despite the most careful treatment, operation becomes a necessity. This is true, also, when—although immediate symptoms may abate—recurrences are frequent in spite of every precaution.

5. *Increase in size of a niche.*—Evidence of increasing size of a niche or failure of the niche to disappear under careful medical treatment is another indication for operation. This is not so because a large niche signifies cancer, but because it indicates a large, indurated ulcer with surrounding reactive or inflammatory changes making healing very difficult. If healing does occur there is no chance for a satisfactory return of gastric function owing to deformity. The patient is usually unable to endure so uncomfortable an existence and welcomes the relief offered by surgery.

6. *Progressive pyloric or duodenal stenosis.*—If delay in emptying becomes increasingly pronounced so that recovery cannot take place and even partial comfort is impossible, the patient should be operated upon. The more complete the stenosis, the more urgent the need for operation.

Associated intra-abdominal disease.—It is well known that when

there is a diseased gall bladder or appendix in conjunction with peptic ulcer, such a diseased organ may be just as responsible for the symptoms which are present as the ulcer itself. Moreover, medical treatment in the presence of such associated disease is of little or no avail. So operation is definitely indicated, but we think that the surgeon should remove the appendix or gall bladder alone if inspection of the ulcer area reveals a small ulcer that is not interfering with the emptying of the stomach.

RELATIVE INDICATIONS FOR OPERATION

Among the relative indications for operation, one must, unfortunately, include the economic status of the individual. When it is impossible for a patient properly to follow treatment, and when the symptoms are of such a degree as to make relief imperative, one must then consider the benefits offered by surgery. It is unfortunate that economic conditions should be one of the determining factors among the surgical indications for peptic ulcer, but it is so, nevertheless, because many patients are so placed in life that a protracted rest-in-bed, medical program cannot be followed. If hospitals and private sanatoria, as well as health resorts with or without spas, were more attentive to dietetic rules, the medical treatment of ulcer would be shortened and more cures effected because more patients could afford to undergo the treatment.

Included in the group of cases in which there are relative indications for operation is the patient with adhesions between the stomach and adjacent organs. These adhesions may be more responsible for the symptoms than the ulcer itself.

In cases in which there is delayed emptying of the stomach due to spasm of the sphincter pylorica rather than to the ulcer itself, medical treatment may be beneficial. If it is not, or if the patient cannot afford the necessarily prolonged medical treatment, operation should be advised.

TYPE OF OPERATION

The aim of surgery in the treatment of peptic ulcer has been to find the type of operation which will meet three requirements, namely, cure of the ulcer, restitution of function, and the lowest possible death rate. A number of operations have been devised with

this three-fold object in view. Chief among these are, posterior or anterior gastroenterostomy; gastroenterostomy with pyloric exclusion; excision and cauterization of the ulcer; sleeve resection; pylorectomy with Bilioth I or Bilioth² II; gastroduodenostomy and modifications thereof, such as the Kocher and Polya procedures; and, finally, subtotal gastrectomy.

GASTROENTEROSTOMY

Gastroenterostomy was devised and introduced by Woelfler³ of Vienna for the specific purpose of relieving pyloric stenosis. A new opening was made in the stomach to connect with the jejunum, thus permitting food to pass into the small intestines without going through the pylorus. Anterior gastroenterostomy was performed at first, but was soon replaced by posterior gastroenterostomy, except in those cases where, for technical reasons, a posterior gastroenterostomy was impossible. Because gastroenterostomy is a comparatively minor operation, with an exceedingly low mortality, and because in the instances (about 70 per cent.) in which the results are satisfactory the patient is enabled to lead a comfortable existence, without digestive disturbances, this procedure rapidly gained favor.

Numerous theories were advanced to explain the favorable results of gastroenterostomy. One was that food is drained directly from the stomach into the small intestines without the necessity of peristalsis on the part of the stomach, thus sparing motor function and reducing acid secretions to a minimum. It seemed reasonable to assume that, the stomach's function being spared, the ulcer would have a chance to heal.

Paterson⁴ attributed the success of the operation to the fact that, following it, there is a decrease of total chlorides in the stomach. Others have attributed the diminished acidity after gastroenterostomy to the regurgitation of intestinal juices into the stomach which alkalinize its contents.

With the advent of the roentgen ray, it was seen that gastroenterostomy does not convert the stomach into a mere drainage tube. Cannon,⁵ and later Cannon and Blake,⁶ demonstrated experimentally on animals that, after gastroenterostomy, the mode of filling, peristalsis and the tendency of the chymified food to pass through the pylorus, are exactly the same as when no gastroenterostomy has

been performed. They showed that after the operation food passes only intermittently through the narrow stoma and that, even when the pylorus is closed by the operation, it reopens after an interval of a few weeks or months. These experimental observations were confirmed in man by clinicians, who demonstrated roentgenologically that shortly after a gastroenterostomy the contents of the stomach pass not only through the new stoma, but also through the pylorus, more often through the pylorus than through the stoma. von Eiselsberg⁷ in Vienna and A. A. Berg⁸ in this country tried to prevent this by suturing the pylorus at the time of the operation for gastroenterostomy, but clinical experience has shown, just as have animal experiments, that in most cases the pylorus eventually reopens. It was found, also, that when the pylorus is excluded, gastric acidity becomes higher because regurgitation of duodenal contents into the stomach is interfered with, and that jejunal ulcers occur more often than after simple gastroenterostomy.

When it was found that there is recurrence of the ulcer or the formation of a new ulcer in about 30 per cent. of cases after gastroenterostomy, and that other complications may result, this procedure began to lose ground and other types of operation were devised. The fact remains, however, that simple gastroenterostomy does relieve the symptoms of ulcer in a great many cases. This may be accounted for by the fact that drainage does exist during the early period following operation, and that, during this period, when food is diverted from the ulcerated area, the stomach empties itself without marked peristalsis and contains a minimum of secretions so that the ulcer has a chance to heal. In our experience those cases in which the favorable results are permanent, the ulcer has healed to such an extent that it does not recur with the return of normal peristalsis and gastric acidity.

EXCISION AND CAUTERIZATION

The first operation devised to remove the ulcer itself was introduced by Balfour⁹ and is still performed by many surgeons for small duodenal ulcers. Most surgeons prefer to use it in conjunction with gastrojejunostomy because excision alone is sometimes followed by adhesions between the point of excision and adjacent organs, leading

to stenosis. If excision with cauterization is performed upon an ulcer on the lesser curvature of the stomach, particularly in the pars media, there is so often incessant vomiting after the operation, causing death unless a jejunostomy is performed, that this procedure has been largely discontinued for this type of ulcer.

SLEEVE RESECTION

Sleeve resection with anastomosis of the upper and lower parts of the stomach was introduced to obviate postoperative vomiting, but has such a high mortality that it is seldom used.

GASTRODUODENOSTOMY

When there is a large ulcer in the duodenum or at the pylorus, resection of the ulcer bearing area, with gastroduodenostomy—that is, attaching the stump of the stomach to the lower part of the duodenum—has the advantage of eliminating the possibility of jejunal ulcer. The gastric contents drain directly into the duodenum, which is more or less accustomed to acid secretions, and is there counteracted by bile and intestinal juices. This is the Kocher¹⁰ procedure. Another procedure is the Polya¹¹ operation which corresponds to the Finney¹² operation and is sometimes called pyloroplasty. The opening is made laterally in the duodenum, taking in the entire pyloric ring, so that a very large opening is provided between the stomach and the duodenum. Finney states that the special advantage of this operation is that the ulcer on the anterior wall of the pylorus or duodenum, or even on the lesser curvature of the stomach near the pylorus, can be very well visualized.

PYLORECTOMY OR PARTIAL GASTRECTOMY

When portions of the pylorus and of the duodenum are removed, the operation is called pylorectomy, or partial gastrectomy. This procedure is usually carried out for a large ulcer on the pylorus or in the first portion of the duodenum. It is sometimes performed in conjunction with a Bilioth I, that is, by connecting the stomach, after the excision, with the lower part of the duodenum. Occasionally it is carried out in conjunction with a posterior gastrojejunostomy, that is with a Bilioth II.

SUBTOTAL GASTRECTOMY

The most radical operation devised for the cure of peptic ulcer is subtotal gastrectomy. It is practiced in this country by A. A. Berg¹³ and others, irrespective of the size or the location of the ulcer; even for a small ulcer in the first portion of the duodenum. Its advocates claim that it not only removes the ulcer proper, but the entire ulcer bearing area; that is, all of the region from just below the incisura angularis to the end of the first portion of the duodenum. However, those who state that the ulcer bearing area must be removed to prevent the formation of a new ulcer would have us believe that the entire area is subject to ulcer formation so that if only the portion containing the ulcer is removed new ulcers can and often will form in the part allowed to remain. The truth is, however, that in the vast majority of cases ulcer is encountered singly, or at most doubly, and that after the healing of one ulcer, by medical or surgical means, another ulcer very seldom forms. It is admitted that subtotal gastrectomy does preclude all possibility of the formation of a new gastric or duodenal ulcer and that it obviates the possibility of marginal or jejunal ulcer to a considerable extent, but the mortality, even in the best hands, is a great deal higher than after any other type of operation. Therefore, we cannot concur in advocating this procedure for every type of ulcer without exception. Rather do we adhere to the wise teaching of Finney and also of Lahey,¹⁴ namely, that the kind of operation is to be determined by the surgeon after he has opened the abdomen, with subtotal gastrectomy reserved for those cases with (1) multiple ulcers, (2) marked deformity of the stomach, (3) an ulcer situated high on the lesser curvature of the stomach, (4) an extremely large ulcer, or (5) an ulcer that awakens the slightest suspicion of malignant degeneration.

The advocates of subtotal gastrectomy lay special emphasis on the fact that this procedure removes the causes of ulcer which are, in their opinion, gastric catarrh and gastric acidity. They base this contention on the fact that in the majority of resected cases of peptic ulcer there is definite evidence of pyloritis. However, we do not believe that pyloritis is a forerunner of ulcer, but a consequence of it. If gastric catarrh or minute, multiple erosions were actually forerunners of peptic ulcer, the postoperative effect of gastroenter-

ostomy would be, in the majority of cases, the formation of a new ulcer in the immediate vicinity of the old ulcer. But this seldom happens. Although the multiple areas of erosion alleged by the advocates of subtotal gastrectomy to be ulcers in the process of formation may be so in some cases, yet in most instances such erosions and the accompanying edema disappear with the subsidence of symptoms. Our clinical studies have convinced us that there is no evidence of actual catarrh in the vast majority of cases, and that when catarrh is present in the vicinity of the ulcer it is usually found during the active stage of the ulcer and disappears with cessation of the activity of the ulcer.

There is no doubt that acidity, especially hyperacidity, is largely responsible for the symptoms of ulcer and can prevent its healing, but in our opinion it is no more a cause of ulcer than is gastric catarrh. After an ulcer has been healed by medical treatment there is as much acid in the stomach as before but the patient experiences no symptoms, and if the ulcer does not heal even normal acidity, but especially the slightest increase in acidity, will so irritate the raw surface of the ulcer that symptoms are produced. But once an ulcer has healed, the acidity in the stomach will not cause another ulcer to appear any more than it caused the first ulcer. However, in such portions of the digestive tract as, for instance, the jejunum or ileum, where acidity is not present physiologically, the gastric contents if they reach this region may be a primary cause of ulcer in this location.

COMPLICATIONS AND SEQUELAE OF GASTRIC OPERATIONS

In order best to understand postoperative management and the prevention of complications, it is essential to know how healing takes place postoperatively.

Marchand¹⁵ has shown experimentally that an incision through only the mucous membrane of the stomach heals readily within a few hours or a day. When glandular structures also are cut, healing takes place within a few days without scar formation. But if the incision extends into the muscular layer a considerably longer period of time is required for healing which occurs by cicatricial contraction, causing deformity. If the serous membrane also is incised, there is an outpouring of fibrin over the serosa which forms dense

connective tissue, causing increased contraction and deformity. Occasionally, instead of the formation of connective tissue, the fibrin softens, breaks down, and delays or prevents healing. If infection occurs in the process of healing, the entire area may suppurate and break down.

Oozing of blood in the stomach proper.—Applying Marchand's experimental findings to gastric surgery in man, it is evident that because the incision must go through all layers, healing takes place slowly and by cicatricial contraction, causing various degrees of deformity. The mucous membrane heals first, but within the first few days there is usually hyperemia in the incised area or its immediate vicinity, and there may be rupture of small capillaries followed by the oozing of small quantities of blood in the stomach. Sometimes the blood accumulates in the stomach until there is sudden hematemesis, which explains why, practically always after operation upon the stomach, if there is postoperative vomiting during the first five or six days, there is some evidence of blood in the vomitus, and why, when there is no vomiting, there is usually occult blood in the stool. When the bleeding comes only from hyperemic areas or from small capillaries, even frank hematemesis need not be alarming unless it is persistent and accompanied by acute dilatation of the stomach with symptoms of collapse.

The symptoms depend upon the quantity of blood that oozes. If small, the patient may experience only distress in the upper abdomen, with regurgitation or vomiting of small quantities of gastric, blood-tinged fluid. After a few days the symptoms subside. But if the quantity is large, there are the usual symptoms of internal hemorrhage.

Leakage of the wound.—Should there be an insufficient formation of granulation tissue within the first four or five days, the stitches in the external suture line may loosen, allowing blood to escape into the surrounding tissues and to form a hematoma which is usually absorbed without further complication. If not absorbed, perigastric infiltration develops which, even though non-suppurative, gives rise to a palpable mass in the region of the wound.

The patient usually complains suddenly of severe pain in the upper abdomen, as well as of burning pain in the wound area. One may be inclined to ignore this particular symptom because there is

usually some pain over the incision after all abdominal operations. However, if the burning pain increases in intensity, it is important to consider the possibility of local infiltration due to wound leakage. Palpation alone is not a sufficient guide to diagnosis because, in nearly all cases, there is local induration along the suture line. There is usually an increased leukocyte count and often an increase of polymorphonuclears to 80 per cent. or 85 per cent. Should the temperature continue to rise, if tenderness becomes more marked and if the leukocyte count increases, it is reasonable to assume that suppuration is taking place, necessitating an early incision in order to prevent further suffering and additional complications.

Atony with or without dilatation of the stomach.—It often happens that within the first forty-eight hours after operation, the patient complains of severe pressure in the upper abdomen. On physical examination one detects tympany over Traube's space and gurgling and splashing in the stomach, the gurgling sound being transmitted over almost the entire heart, indicating the presence of air and fluid. If, during this stage, the patient is relieved by gastric lavage, the more severe complication of atony with acute dilatation of the stomach may be prevented. If the symptoms are not heeded, the patient may, within the next twelve hours suddenly begin to vomit large quantities of gastric secretions and even regurgitated intestinal contents; symptoms of collapse may come on indicating acute dilatation of the stomach due to progressive atony.

Aseptic subphrenic inflammation.—Occasionally, during the first or second week after a gastric operation, pain develops in the left or right hypochondrium, accompanied by moderate elevation of temperature and diminished breathing at the base of the lung on the affected side, with roentgenologic manifestations of an elevated diaphragm. These findings awaken the suspicion of a subphrenic abscess, but, after a few days or possibly weeks, the patient makes a complete recovery, indicating that the condition was an aseptic inflammation. In most cases, this aseptic inflammation gives rise to postoperative adhesions.

Subphrenic abscess.—A complication that is still fairly frequent is right or left subphrenic abscess, more often left-sided, occasionally bilateral. The abscess may occur in any anterior or posterior sac or in the omental bursa. Although symptoms may appear as early as

the second or third week, complete evidence of suppuration may not present itself until the third or fourth week, sometimes not until the patient has left the hospital.

The first symptom is pain in the upper abdomen, greater on the affected side, with almost typical phrenic nerve radiation. The severity of the pain varies from mild to intense, which is very misleading. There is a non-productive cough which causes pain over the lower part of the chest. This pain on coughing may be so severe that the patient suppresses the cough in order to avoid the pain. The condition progresses slowly and for weeks may be erroneously diagnosed as an infection of the pleura or base of the lung.

One of the earliest physical signs is diminished breathing at the base of the lung on the affected side. This is due to atelectasis which is caused by elevation of the diaphragm. There is therefore diminished respiratory excursion of the base of the lower lobe of the lung on the affected side, and there is flatness over the base of the lung. As the condition progresses, fluid begins to accumulate in the pleura, the so-called "sympathetic effusion," which seldom becomes purulent. There is tenderness on palpation of the affected side, aggravated by forcible pressure laterally over the lower ribs. An erroneous diagnosis is sometimes made of a primary infection of the lungs or pleura. However, in sympathetic effusion there is resonance in the lower axilla and tympany over the lowermost part of the axilla, due to the presence of air at the top of the abscess.

If the abscess is neglected it may break into a neighboring organ. For instance, a left-sided subphrenic abscess may break into the spleen causing suppuration of the spleen; a right-sided abscess may break into the liver, causing a liver abscess; or the abscess may break into the peritoneal cavity or into the retroperitoneal space, giving rise to localized or generalized peritonitis.

Hiccoughing.—During the first few days after gastric operation, hiccoughing is sometimes a very alarming symptom. It is not necessarily due to peritonitis, but may be caused by a little infiltration around the wound, by irritation of the vagus nerve, or by spasm of the diaphragm. It is very exhausting to the patient, whatever the cause may be, and gives him no chance to sleep. It may even lead to circulatory failure.

Generalized peritonitis.—The outstanding symptoms of general-

ized peritonitis are: facies Hippocratica, wet cold skin, rapid thready pulse, and a climbing temperature. Vomiting is rare because of the abdominal pain, but there may be regurgitation of brownish, blood-tinged fluid having a decomposed odor. The tongue is parched; thirst is extreme. The abdomen is distended, rigid, and extremely tender. The blood pressure is very low and an extreme leukocytosis is a most important finding. The condition usually terminates with extreme cardiac weakness or edema of the lungs.

Massive collapse of the lung.—Of the many pulmonary complications, the earliest is massive collapse of the lung. Although this is a very alarming complication, sometimes fatal, it is often possible to prevent it or treat it successfully if it is diagnosed early.

The symptoms are: severe dyspnoea, cyanosis, extremely rapid respirations, rapid and thready pulse, and an elevation of temperature, sometimes to 103° F. or 104° F. There may be vomiting, simulating an intra-abdominal complication, but the fact that the breathing is entirely abdominal speaks against such a diagnosis. There is not much pain.

Physical examination reveals dulness over almost the entire affected side. The breath sounds are diminished or absent, simulating effusion, but, in contradistinction to effusion, the heart is not pushed to the opposite side, but is pulled toward the affected side. If the collapse is of the left lung, the apex beat of the heart is palpable and the heart sounds are heard in the left axilla; if the right lung has collapsed the apex beat may be palpable in the epigastrium.

The roentgen ray examination reveals a diffuse shadow on the affected side without lung markings. The heart is pulled toward the affected side, and the dome of the diaphragm on that side, although seen only indistinctly, is considerably elevated. Fluoroscopically, one can see the entire mediastinum move on inspiration toward the affected side.

Postoperative pneumonia.—Although this is a much more frequent complication than massive collapse of the lung, it does not occur as a rule until from three to five days after operation.

The symptoms and treatment are too well known to need description.

Pulmonary embolism with or without infarction.—This is still, unfortunately, not an uncommon occurrence, particularly after gas-

tric operations. It occurs usually just as the patient begins to sit up or get out of bed, some ten or twelve days after operation. The effect of the embolus depends upon whether it obliterates a small or a large pulmonary vessel. If a small one, the symptoms may be so insignificant as not to be recognized except possibly by the fact that the patient has experienced a sudden, brief sensation of uneasiness in the chest with moderately increased respirations, a moderate elevation of temperature, and some increase in pulse rate. There may also be a slight cough.

Should the embolus obliterate a vessel of large size the immediate symptoms are: sudden severe pain in the chest with marked dyspnoea, increased respiratory rate, elevation of temperature, rapid pulse, and a cough that, at first, is dry and non-productive. As a large embolus is usually followed by pulmonary infarction, hemoptysis and sometimes expectoration of large quantities of blood—true hemorrhage of the lung—may occur. There is generally a reactive pleurisy so that definite friction can be detected and in some cases palpated. Where the pleurisy is not marked, crepitant rales, diminished breathing or broncho-vesicular breathing, and egophany are present over the affected area. The infarct may be completely absorbed or it may give rise to hemorrhagic effusion lasting for weeks, sometimes necessitating operation. Although the effusion is never large enough to call for aspiration, the pain may be so severe as to require it. Very rarely does the infarct suppurate and give rise to lung abscess or to gangrene of the lung. Generally, absorption of the effusion takes place, the healing of the infarcted area requiring a considerable time.

If the infarction extends from the region of the hilum to the periphery, the roentgen ray examination nearly always reveals a triangular shadow with the base of the triangle toward the hilum.

When the embolus is so large that it obliterates a large pulmonary artery, death may be instantaneous or be preceded by extreme pain in the chest, inability to catch the breath, extreme cyanosis, and cold perspiration. The patient may scarcely have time to call for aid before death occurs. There is a blocking of the pulmonary circulation which interferes with the oxygenation of the arterial blood so that the blood pressure falls suddenly and there is anemia of the brain.

COMPLICATIONS AND SEQUELAE OF GASTROENTEROSTOMY

Each of the operations for peptic ulcer has its peculiar complications. Gastroenterostomy has been criticised because it may be followed by unpleasant sequelae from within a few months to many years thereafter. Because such sequelae have been rather frequent and are actually the result of the gastroenterostomy, Pribram¹⁶ has called gastroenterostomy a disease. However, if the operation is performed when indicated this is much too pessimistic a view.

The main complications of gastroenterostomy are: (1) Disturbances in mode of emptying,—either too rapid emptying due to the large gastroenterostomy opening, or delayed emptying due to atony of the stomach or spasm of the stoma; (2) recurrence of the old ulcer; (3) formation of a new peptic ulcer; (4) formation of a gastrojejunal or jejunal ulcer; (5) the "vicious cycle"; (6) gastrocolic or jejunal fistula; and (7) adhesions.

Too rapid emptying of the stomach.—It is well known that, for the first few months after gastroenterostomy, there is a strong tendency for the stomach to empty itself very rapidly through the gastroenterostomy opening. There is a minimum of peristalsis during this period so that the stomach empties almost by drainage, which may be nature's effort to spare the stomach. Only when the new stoma acquires sphincteric action does the stomach again undergo peristalsis, after which time it empties almost as does the normal stomach.

Catarrh of the small intestines.—Due to the too rapid emptying, the food is poorly digested and may cause catarrh of the small intestines, giving rise to symptoms of distress an hour or two after meals. The distress is particularly felt in the mid-abdomen and there is sensitiveness to pressure to the left of the umbilicus. There is also a sensitive area over the left side of the spine in the region of the second lumbar vertebra. Because of this left-sided pain, gastrojejunal or jejunal ulcer is suggested. However, there is never any interdigestive pain in these cases as there is in gastro-jejunal or jejunal ulcer. The patient complains of considerable gurgling in the mid-abdomen and there is loss of appetite and weight. Periods of comfort alternate with periods of distress, the latter being brought on by the slightest indiscretion in diet, particularly when fats are eaten. Not infrequently the stool contains macroscopic and micro-

scopic fat globules and microscopic fatty acid crystals, simulating the findings of gastro-colic or jejuno-colic fistula. There is no visible mucus on the surface of the stool and there is no blood in the stool, except when there is associated catarrh of the colon.

Upon making a roentgen ray examination, one finds that two hours after ingestion of the contrast meal, a large part of it has reached the ascending colon and that some is in the small intestines. If the contrast barium meal does not reach the ascending colon in two hours, Porges¹⁷ has found that a heavier meal consisting of eggs, meat, etc., in addition to the contrast meal, will increase the motility of the small intestines so that the food reaches the ascending colon within this time.

Catarrh of the larger bile ducts.—A complication that may occur secondary to intestinal catarrh as a result of the too-rapid emptying of the stomach is catarrh of the larger bile ducts. Sometimes there is even the formation of gall stones secondary to the intestinal catarrh. This is thought by Porges to be due to the fact that because of the intestinal catarrh the permeability of the intestinal wall to bacteria is enhanced. Hence entrance of bacteria through the portal circulation into the liver is possible, leading to infection of the bile ducts and, in some cases, to the formation of gall stones. Porges quotes cases in which operation for gall stones was required within a year or two after gastroenterostomy, although at the time of the gastroenterostomy the gall bladder had been found to be normal. Our experience confirms this observation.

Typhlitis.—Occasionally, due to very rapid emptying of the stomach and the ensuing catarrh, typhlitis develops. This is often mistaken for appendicitis. Diagnosis is of the utmost importance for the reason that these cases can be managed by proper medical treatment without recourse to surgery.

Delayed emptying due to atony.—Occasionally there is marked delay in emptying due to atony of the stomach, which may have existed before the operation or may have developed thereafter. The outstanding symptoms are a sense of fullness and pressure in the epigastrium, sometimes extending into the throat, after only a few morsels of food. There is a strong inclination to belch or regurgitate food and sometimes the patient must relieve himself by induced vomiting, spontaneous vomiting rarely occurring.

Fluoroscopically, one observes that the gastroenterostomy opening functions well, food being seen to leave the stomach through this opening during the early part of digestion. Complete emptying of the stomach, however, is delayed beyond normal time. Four, five, or six hours after a meal the greater part of the food may still be in the stomach. The stomach has all the characteristics that go with atony, namely, a very large air bag, the fornix does not hold the food at all, and the lower part of the stomach is considerably distended since peristalsis is either absent or very superficial. In most cases the stomach is ptosed so that the greater curvature is several inches below the crest of the ilium.

Delayed emptying due to spasm of the stoma.—It is remarkable that sometimes after years during which the stoma has functioned properly or with food going through both the pylorus and the stoma, the patient complains suddenly of gastric distress and of pain that comes on immediately after eating and increases in intensity as the process of digestion goes on, until it reaches its height after three or four hours. There is often spontaneous vomiting, the vomitus consisting of sour gastric contents, markedly acid in character, and often containing thoroughly chymified particles. The appetite is usually good, but the patient is afraid to eat. There is tenderness over the entire upper abdomen, and one is suspicious that the patient has a marginal or jejunal ulcer. Real interdigestive pain, however, is absent, and the sensitiveness to pressure is not localized, as it would be in jejunal ulcer.

The roentgen ray examination reveals that, although the food has a tendency to pass through the stoma, or through both the pylorus and stoma, its passage is delayed. The food passes through in a very thin stream and sometimes has to be forced from the stoma into the jejunum by the palpating hand. There is considerable residue three, four, and even five hours after a meal, depending upon how well the pylorus functions. Should it function poorly, there may be a residue ten, twelve or even twenty-four hours after a meal, simulating complete stenosis.

Recurrence of the ulcer.—In view of the fact that the ulcer is not removed by gastroenterostomy, there is a possibility that it may recur. This is particularly true of ulcer on the lesser curvature of the stomach or duodenum, if the ulcer was non-stenosing and in a

florid state at the time of operation. The recurrence of symptoms typical of peptic ulcer may occur early or late after the gastroenterostomy, often following a period of apparent healing of the ulcer.

Occurrence of a new ulcer.—We have found that this is far less frequent than a return of symptoms due to recurrence of the old ulcer. Should a new peptic ulcer form, however, the symptoms and signs do not differ from those caused by the original ulcer for which operation was performed.

Marginal or jejunal ulcer.—It has been found that jejunal ulcer occurs in from 20 per cent. to 30 per cent. of cases in which gastroenterostomy has been performed. It is most likely to occur in the afferent or efferent loop, or just at the ring of the new stoma, in which event it is called a marginal ulcer. Once it was thought that pyloric resection would lower the percentage of jejunal ulcers, but this did not prove to be the case. It was reasoned that, inasmuch as the action of the pylorus stimulates the acid cells in the corpus, resection of the pylorus would remove the acid factor that cause jejunal ulcer. It was found, however, that after resection of the pylorus gastric acidity is as high, or higher than before.

Jejunal ulcer generally occurs between one and four years after the operation, although it can occur much earlier or much later. Carman¹⁸ has reported its occurrence twenty-one years after operation.

The cause of marginal ulcer, as pointed out by the W. J. Mayo¹⁹ and by Moynihan,²⁰ is non-absorption of sutures, whereas jejunal ulcer is attributed by some authors to an injury of the jejunum at the time of operation which predisposes the area to ulcer formation. We are unable to accept this explanation because jejunal ulcer does not follow gastroenterostomy for gastric cancer, although here, too, the jejunum may be injured at operation. An important cause of jejunal ulcer, we believe, is the fact that the jejunum is not accustomed to the acid gastric chyme. Normally gastric secretions are neutralized by regurgitation of the intestinal contents through the pylorus and duodenum. If, for some reason, this regurgitation is disturbed so that the neutralizing effect is diminished, the gastric acid contents reach the jejunum in its afferent or efferent part, stagnate there, and cause, first, irritation and, later, ulcer. The lack of regurgitation of jejunal contents into the stomach to bring about

neutralization may be due to a functional disturbance in the jejunum, which would explain why symptoms of gastric distress, due to catarrh in the jejunum, may precede the formation of a jejunal ulcer.

One of the most typical symptoms of jejunal ulcer is that there is a period before the actual symptoms begin in which the patient complains of vague gastric disturbances. These vague symptoms consist of distress in the upper abdomen and loss of appetite and weight. The loss of weight and appetite is due to disturbance in the absorption of food in the small intestines as well as to disturbance in the assimilation of food. This loss of weight is more pronounced in jejunal than in marginal ulcer. As the ulcer develops, interdigestive pain appears three or four hours after a meal, relieved by food, but not so completely alleviated as is the pain of peptic ulcer. The patient often points directly to the seat of pain as being one, or one and a half inches to the left of the umbilicus. Periodicity is not concurrent with seasonal changes. There may be symptom free intervals of but two or three weeks.

Palpation reveals a sensitive pressure point one to one and a half inches to the left of the umbilicus, aggravated by deep pressure. There is considerable tenderness in this area, which is increased by the patient's taking a deep breath, or by holding his breath, which brings the seat of the ulcer nearer the surface.

The gastric contents are hyperacid, very rarely subacid. Occult blood is seldom seen in the stomach contents, although it may appear in the stool. It is highly important to remember that jejunal ulcer is subject to severe hemorrhage, less frequently to perforation, and still less often to jejuno-colic or gastrojejunocolic fistula.

Fluoroscopic examination—using a thin barium suspension meal—is indispensable for diagnosis. In a large number of cases, the food is seen to pass through both the stoma and the pylorus, although during the very early part of digestion, that is during the first half hour, so much goes through the pylorus that it is difficult to detect any going through the stoma. If the patient is examined in the erect, prone, antero-posterior, oblique and lateral positions, with the palpating hand over the stomach, food can be forced into the jejunum, which is then seen to be irregular in outline. The presence of a niche is detected with great difficulty, when films are taken, but its detection especially with indentation opposite it is, of course,

absolute evidence of ulcer. We believe that the study of the mucous membrane by means of a barium suspension meal is important, particularly in view of the difficulty of visualizing the niche. When there is an ulcer, the mucous membrane is distorted in the region of the ulcer and has definitely converging folds towards the ulcer. Deformity and dilatation of the loop in the region of the ulcer simulating a diverticulum are additional signs of ulcer. In many cases, there is associated spasm of the stoma so that there is marked delay in emptying of the stomach. There may be, also, considerable atony of the stomach. Hyperperistalsis is not diagnostic except to indicate gastric irritation.

Gastrojejunal or gastrocolic fistula.—Each of these complications of gastroenterostomy is recognizable with ease. The important clinical manifestations are persistent loss of weight and appetite, with periodic attacks of diarrhea preceded by slight intestinal cramps confined to the mid-abdomen. There is slight tenderness on palpation of the mid-abdomen. In some cases there is regurgitation from the colon into the stomach, causing fecal vomiting, which, of course, establishes diagnosis beyond doubt. The stool shows undigested particles of food, and an excess of fat as first pointed out by H. Strauss.²¹ A case has been reported of jejuno-colic fistula after gastroenterostomy in which one of the outspoken symptoms was night blindness (nyctalopia), which was attributed by Wilbur and Eusterman,²² reporting the case, to Vitamin A deficiency.

One is often surprised when fluoroscopically observing the passage of food from the stomach into the intestines to see that a great deal of the meal finds its way into the transverse colon within five or ten minutes, and that very little passes through the stoma into the efferent jejunal loop. Diagnosis may escape one entirely if films are taken only during the first hour. After three or four hours, the entire communication between stomach, jejunum and transverse colon becomes apparent, the stomach and transverse colon appearing well filled with contrast meal while the jejunal loop contains only a thin opaque stream.

In some cases, however, the small intestines are filled with the major portion of the meal while a small amount only is visible in the transverse colon. For two, four, or even six hours one may be unable to ascertain with certainty that there is a communication between the

jejunum and the transverse colon. After twenty-four hours, however, the stomach, jejunum, and transverse colon all contain contrast meal so that the roentgenologic evidence is positive for fistula. It is important in all cases to give a contrast enema, for such an enema is invariably seen to go into the transverse colon and thence through a loop of small intestine into the stomach.

"Vicious Cycle."—One of the phenomena sometimes following gastroenterostomy, either soon or years thereafter, is persistent regurgitation and vomiting, termed the "vicious cycle." The vomitus contains more or less bile and cannot be controlled by gastric lavage. Moynihan²⁰ has described four varieties of vicious cycle:

1. Regurgitation of duodenal contents through the pylorus;
2. Escape of fluids from the stomach into the afferent loop;
3. Escape of fluids from the efferent loop into the stomach (commonest and gravest variety); and
4. Regurgitation of contents from the afferent loop into the stomach.

The causes of such regurgitation have been studied experimentally by Chlumski,³² who reports that it may be due to:

1. A sharp kinking of the afferent and efferent loops causing a spur to form at the point of juncture;
2. Jejunal displacement, sometimes producing a kink at the duodeno-jejunal juncture which causes duodenal obstruction;
3. The mucous membrane of the stomach may form large, pouching valves that obstruct the afferent opening;
4. Closure of the anastomotic opening by an improperly applied stitch;
5. Compression of the afferent loop by the colon;
6. Constriction of the afferent loop by an opening in the transverse mesocolon; and
7. Antiperistalsis of the implanted jejunum.

Adhesions.—Gastroenterostomy is sometimes followed by adhesions in the region of the stoma. The symptoms depend upon the extent of the adhesions. If they involve the jejunum in the vicinity of the juncture of the stoma, they may lead to complete obliteration

of the stoma. If no food empties through the pylorus, this obliteration of the stoma means complete obstruction, and treatment is, of course, surgical.

COMPLICATIONS AND SEQUELAE OF THE BALFOUR OPERATION AND OF PYLOROPLASTY

If the ulcer is so large that the excised area is extensive, marked deformity of the stomach is likely to follow and interfere with gastric function. Pyloroplasty has been followed by extensive connective tissue formation and secondary pyloric stenosis; it is also often followed by peripyloric and periduodenal adhesions.

COMPLICATIONS AND SEQUELAE OF SUBTOTAL GASTRECTOMY

The strongest claim made on behalf of subtotal gastrectomy is that since it removes not only the ulcer, but largely, also, the ulcer bearing area, and does away with the possibility of acid secretion, new ulcers do not occur.

Cases of jejunal ulcer forming despite a subtotal gastrectomy have been reported in the literature. Dibold²⁴ has recently reported seven cases of jejunal ulcer following gastric ulcer. He does not state whether there was subtotal or a small resection, but these seven cases did occur out of a total of forty-two and had to be operated upon again. Dibold states also that occasionally after resection the part of the stomach that is left gives rise to a great deal of catarrh, largely due to the fact that the patient's diet has not been satisfactorily followed after the operation. In our own experience, we have seen patients suffer rather severely from gastro-intestinal symptoms, but directly attributable to the fact that practically all of the function of the stomach was removed by the subtotal gastrectomy. In one of our cases, diarrhea was very marked, the stools containing a considerable quantity of fat and muscle fibers. In another case, there was considerable anemia, not of the "pernicious" type, but of the inanition or alimentary type. It was impossible to influence these patients favorably by hydrochloric acid which, in reality, caused greater discomfort. Dibold reports four cases of severe anemia developing several years after gastric resection, and instances of real pernicious anemia after subtotal gastrectomy have been reported from the Mayo Clinic by Conner and Birkeland.²⁵

It is thought by some that gastro-intestinal distress following subtotal gastrectomy may be due to a disturbance of the external secretory function of the pancreas, as demonstrated by an increase in diastase in the serum and in the urine and a diminution of diastase and trypsin in the duodenal contents. It has been advised to give pancreatic preparations for these symptoms. The fact cannot be denied that occasionally the pancreas is damaged during operation, with corresponding symptoms. But we have not encountered functional disturbance of the pancreas as a result of the operation, without traumatic injury to the pancreas.

POSTOPERATIVE TREATMENT

Realizing that during the process of healing any food that stimulates secretions or peristalsis will interfere with the process of healing, one must allow no food whatever by mouth during the first few days. It is a well demonstrated physiological fact that if food is not allowed for two or three days, even hunger contractions will cease, so that the stomach is perfectly at rest. During the first few days all fluids must be administered by rectum, by hypodermoclysis, or intravenously if shock is great or dehydration present. When inanition is marked before operation, 250 cc. of 10 per cent. to 20 per cent. glucose should be administered intravenously every twenty-four hours for three or four days, or until the patient can take carbohydrates by mouth. The rectal administration of glucose by the Murphy drip method may be given, and there is no doubt that a great part of this is absorbed as has recently been shown by Collens and Boas.²⁶ It is important to know that glucose by rectum does not stimulate peristalsis. There is one disadvantage, however, and it is that the Murphy drip method causes great irritation of the rectum as well as abdominal distention. Should the patient complain of these symptoms, the Murphy drip should be immediately discontinued.

Regarding the kind of fluids, it has been the custom to administer either a physiologic salt solution intravenously, by hypodermoclysis, or by the Murphy drip method, or a hypertonic salt solution by rectum. We believe a salt solution is of advantage only if there is actual evidence of a diminution of chlorides in the blood. If the patient vomits excessively after operation, or if he vomited a great

deal before, sodium chloride solution is indispensable to replace the chlorides lost by vomiting and to prevent alkalosis. But if there has been no excessive vomiting and if there is no evidence of a marked diminution of chlorides, one greatly increases the thirst of the patient by administering salt solution. It is much better to give Ringer's solution, which contains both calcium chloride and sodium chloride, and which, even when given by hypodermoclysis or enteroclysis, has a tendency to quench thirst.

If, within the first two or three days, the patient's condition shows signs of dehydration or marked exhaustion we believe a blood transfusion of 250-300 cc. should be given, before serious complications develop.

Should the patient vomit gastric secretions, even though small in quantity and not containing much blood, it is to be remembered that this vomiting can and does prevent healing of the wound and strains the musculature of the stomach. Therefore in these cases a small, thin tube should be introduced through the nose into the stomach so that the gastric contents can be aspirated by continuous lavage until vomiting ceases. This is a much safer procedure than the injudicious use of morphine which causes pylorospasm and intestinal paresis, and interferes with urinary secretion. Morphine should be resorted to only when pain is otherwise uncontrollable.

During the period when the patient receives no food by mouth, the mouth should be rinsed several times a day to prevent parotitis. At most, one may allow small pieces of ice to dissolve in the mouth. If the patient has not vomited within the first forty-eight hours, it is reasonable to assume that the hyperemia in the mucous membrane will have begun to subside so that the patient may drink small quantities of water every half hour. If the patient's condition requires more fluid than this small quantity, the additional amount may be supplied by hypodermoclysis, enteroclysis, or intravenously.

It is essential to examine the stool daily for occult blood. Occult blood known to come from the stomach indicates that healing is not complete, and so until it disappears from the stool the patient should be permitted no food by mouth. It is our belief that if sufficient care is taken during this stage, many gastric sequelae will be prevented, as will also jejunal ulcer.

Method of feeding.—The first articles of food to be allowed

should be yolk of egg and well diluted milk because these substances tax gastric digestion least. The milk should be diluted with lime water (15 cc. lime water to 100 cc. milk) because lime water adds the calcium which dilution of milk with water alone would remove. The patient is allowed hourly feedings: 2 oz. milk one hour, the yolk of an egg the next hour. Sugar, or milk-sugar which serves, also, as a mild laxative, should be added to the milk.

After four or five days, if there has been no ill effect from this diet, one may increase the interval of feeding and the quantity of food. Milk is given in full strength, 4 oz. every other two hours, with a whole egg allowed in the alternate two hour period. In another two or three days—the patient feeling better—half an ounce of sweet cream may be added to each four ounces of milk, a whole egg being given every two hours. Our principle is that during the stay in the hospital, carbohydrates and fats should predominate in the diet.

The administration of vitamins should not be ignored. At the end of fourteen days the patient should be receiving orange juice, grape fruit juice, tomato juice, and lettuce with olive oil. Feeding should be every three hours, now, the patient being put on the second week of the Sippy diet, consisting of thin cereals cooked in milk in a double boiler, warm milk with sweet cream, soft boiled eggs and white bread, toasted, or zwiebach, buttered with sweet butter.

When the patient has left the hospital—irrespective of the type of gastric operation that was performed—the internist should take charge of the dietetic regime. We feel that if the attention of the internist to postoperative dietetic regime were as strict as that of the surgeon toward sepsis and other factors, many a recurrence of ulcer would be eliminated.

The routine Sippy diet should be maintained for several weeks, the patient being cautioned to avoid all foods that stimulate gastric secretion, such as beef, spinach, alcoholic beverages, ice cold drinks such as lemonade, extremely hot drinks, and raw fruit. We have found that an unexplained neuritis may occur after operation due to a Vitamin B deficiency, which has resulted from the patient's long period of dieting before operation. Hence Vitamin B should be stressed in the diet; if necessary, it should be given directly in the form of yeast.

PREVENTION AND TREATMENT OF PULMONARY COMPLICATIONS

In order to prevent pulmonary complications, particularly massive collapse of the lung, active respiration should be encouraged and particularly deep inspiration during the first three or four days. Tight bandaging of the abdomen necessarily interferes with breathing so that most surgeons are against its use. The free employment of morphine makes respirations shallow so that the possibility of pulmonary collapse is enhanced. Therefore, this should be avoided if possible. The inhalation of carbon dioxide with oxygen (5 per cent. CO₂ with 95 per cent. oxygen) is of great aid, serving, also, to prevent postoperative pneumonia which usually implants itself on localized atelectasis at the base of the lung.

Band and Hall²⁷ advocate the substitution of nembutal for morphine and atropine as preoperative medication, with the anesthetist proficient in the use of carbon dioxide to maintain deep, regular breathing. Sedative drugs are to be prescribed after operation as sparingly as possible in order to give the bronchial tree a chance to empty itself. These authors recommend, if collapse does occur, the inhalation of 10 per cent. carbondioxide with 90 per cent. oxygen at hourly intervals. If this method fails, the bronchoscopic removal of mucus from the bronchi is the next procedure to be advised.

PREVENTION AND TREATMENT OF POSTOPERATIVE EMBOLI

Many suggestions have been offered for the prevention of postoperative emboli, but none has actually solved the problem. Small doses of thyroid extract by mouth three times a day are advocated at the Mayo Clinic, the idea being that thyroid extract stimulates the heart to more rapid activity, thus preventing slowing of the circulation and the stagnation of blood in certain parts of the vascular system. In other clinics, it is advocated to change the patient's position fairly frequently in order to improve circulation. We doubt the efficacy of any measure because an embolus will occur when one least expects it, despite preventive measures, especially following gastric operation.

When an embolus does occur, the patient should be given morphine at once. If the patient is extremely cyanotic he should be put into an oxygen tent. In some clinics, leeches are applied over

the area of the vein, on the theory that the hirudin contained in the leech may diminish coagulation of the blood and thus exert a favorable influence.

Great attention must be paid, during the patient's stay in the hospital, to the condition of the peripheral veins, particularly the femoral and saphenous veins, because an embolus to the lung may result from a thrombus in one of these veins. If thrombosis is present, the patient must be kept at rest under local treatment for the pain until all symptoms of thrombophlebitis have disappeared. It is important to remember the clinical fact that when the local symptoms of thrombophlebitis are least pronounced, emboli are most apt to occur. That is, if there is a thrombus in the femoral or saphenous vein which is asymptomatic and discoverable only by palpation of the vein, it is much more apt to be followed by an embolus than is an inflammatory thrombus, or thrombophlebitis with associated lymphangitis. This is explainable by the fact that the inflammatory type of thrombus is adherent to the wall of the vein whereas the non-inflammatory type of thrombus is at least partially free. It is essential routinely to palpate the femoral and saphenous veins for an existing thrombus.

TREATMENT OF PULMONARY INFARCTION

Under rare conditions, a pulmonary infarct may suppurate, form an abscess, or even become gangrenous, necessitating surgical intervention. If there is clinical evidence of gangrene of the lung, the sputum should be examined microscopically for spirochetes. The spirochetes may not be primarily responsible for the gangrene, but the aspiration of spirochetes with the sputum through the bronchi into the gangrenous area of the lung will prevent healing. If spirochetes are found, treatment should consist of small doses of neosalvarsan (not more than 0.1) intravenously every other day for several days.

TREATMENT OF HICCOUGH

Morphine does not afford much relief for hiccupping for as soon as the patient awakes the hiccoughs return. Pulling the tongue forward for half a minute while the patient holds his breath may relieve the patient for several hours, the process being repeated if the

hiccoughs return. Holding a spatulum against the pharynx so that the patient gags actively for from fifteen to thirty seconds is another method of giving relief, the process being repeated as often as may be necessary.

Should these measures prove ineffectual, the passage of a stomach tube may be helpful since it causes the patient to gag sour secretions from the upper end of the stomach into the mouth. Should considerable quantity of secretions be obtained through the tube, it is advisable to wash the stomach actively with luke-warm water to which a little bicarbonate of soda has been added. If none of these measures succeed, the inhalation of carbon dioxide for a few minutes at intervals will almost certainly cure the hiccoughs. The intramuscular injection of 5 cc. of ether is also beneficial.

TREATMENT OF DISTURBED MOTILITY

Too rapid emptying due to atony.—If the food goes through the stomach too fast the stomach has no opportunity to prepare it for intestinal digestion. Hence it is essential that the patient partake of small quantities of food of a nature to require least gastric digestion in order not to over-burden the digestive function of the small intestines. Proteins tax gastric digestion most and so should be avoided. If proteins are given, it should be in the form of peptonized milk. The diet should contain starchy foods and emulsified fats, such as cream and butter. Fruit juices, cocoa, chocolate, coffee and vichy may be allowed. If there is diarrhea it may be necessary to withhold milk for some time, giving, instead, chocolate or cocoa prepared with plain water, to which the yolk of an egg or two has been added.²⁸

Where there is catarrh of the small intestines, it is essential to keep the patient in bed for several days or a week, on an extremely bland diet, consisting chiefly of gruel, especially strained barley. Should gall stones have formed, the treatment is, of course, surgical.

The variety of food in these cases is to be guided by the sensations of the patient. Improvement of appetite and a desire for variety are signs of general improvement so that one may begin to extend variety and quantity, always guarding against overburdening the stomach. As variety and quantity are increased, the intervals between feedings should be lengthened, returning to three meals a day as quickly as possible, allowing perhaps one intermediary meal.

If the patient has a great deal of pain during the first few days, heat should be applied to the stomach by means of a warm electric pad several times a day, half an hour to an hour at a time.

It is remarkable that when the patient has fully recovered, there is no recurrence of symptoms indicating that the condition was not systemic but due largely to a general neurosis.

Delayed emptying due to atony.—Delayed emptying and gastric irritation as a result of atony are resistant to treatment, but with perseverance on the part of the physician and cooperation on the part of the patient, medical treatment does often bring about a satisfactory result.

There is usually a general loss of body weight and a general breakdown of body functions, for which reason it is essential to treat the general condition as well as the local condition. Methods to increase the patient's appetite are necessary. To this end, the patient should be given 10-15 units of insulin, twice daily. Immediately after the insulin, he is given the juice of one orange, sweetened, in order to prevent symptoms of hypoglycemia. Half to three quarters of an hour later a substantial carbohydrate meal is given in the form of cereals, custard, or home-made coffee cake or sponge cake, well buttered, cocoa, and buttered toast. When the patient's appetite responds favorably to insulin, which is continued for two weeks, the battle is won. Should the patient be unable to tolerate insulin, one should give a hypodermic injection of strychnine, arsenic and iron every other day.

It is essential to give a minimum of liquids. The food should be semi-solid in order to prevent distention of the stomach. The meals should be frequent and small in quantity and fluids that are allowed should be given between meals.

Stomach lavage may have to be employed during the first few days of treatment, twice daily perhaps—just before retiring, and in the morning before the first meal. As a rule, lavage is necessary during only the first four or five days. A pint of water is used, to which two or three teaspoonfuls of bicarbonate of soda have been added. If emptying of the stomach continues to be markedly retarded, as evidenced by fullness after meals or by the regurgitation or vomiting of food, dry lavage of the stomach—aspirating the

stomach contents morning and night, should be carried out for three or four days.

Delayed emptying due to spasm.—When delay in emptying is due to spasm of the stoma, it is usually accompanied by acid regurgitation and by a demonstrable increase in gastric acidity. The beginning of treatment, therefore, should be like that for florid peptic ulcer, which means the almost total abstinence from stomach feeding for the first three or four days, all food being given by rectum. If the acidity is high, and the roentgen ray examination shows marked gastric retention, gastric lavage with an alkaline solution should be administered every morning. During this period, a warm electric pad should be applied to the abdomen three or four times a day, one hour at a time. Atropin sulphate 0.0059 should be given twice daily.

When feeding is begun by mouth, the first food allowed is 250 cc. warm milk every two hours and one tablespoonful of olive oil twice daily. After four or five days, the regular second week of the Sippy treatment is begun. Lavage of the stomach should be discontinued at the end of the first week. It is advisable to caution the patient to observe his diet for three or four months. As the condition is usually associated with general nervousness, nerve sedatives and mild hypdrotherapeutic procedures may be necessary. In this condition successful treatment may entirely do away with the symptoms which may not recur. Recurrence depends much more upon physical factors than upon dietetic error.

There is often spastic constipation, which may lead to mucus in the stool causing colica mucosa. This can be treated satisfactorily only by olive oil enemata, 6 to 8 oz. administered before retiring, to be retained overnight. Next morning after evacuation of the oil with the stool, a low enema of two glasses of water and one teaspoonful of salt should be given in order to wash away the fatty acids which may irritate the intestines during the course of the day. If this treatment is continued for from four to six weeks the spastic constipation can be overcome. After this time, it may be necessary to use the treatment once a week, or at most twice a week, then once in two weeks, and eventually once every month or two. This is the best method of treating the condition because laxatives taken by mouth aggravate it.

TREATMENT OF RECURRENT OR NEW PEPTIC ULCER

When it is determined that an ulcer has recurred, medical treatment for peptic ulcer should be started at once. If the ulcer does not respond to the treatment, surgical intervention is indicated.

If a new ulcer forms, operation is called for, subtotal gastrectomy being indicated.

TREATMENT OF JEJUNAL OR MARGINAL ULCER

The presence of marginal ulcer indicates surgical intervention. On the other hand, an effort may be made to administer medical treatment for jejunal ulcer. Should the response not be satisfactory, surgical intervention is necessary.

TREATMENT OF THE "VICIOUS CYCLE"

Treatment for the complications of the "vicious cycle" depends upon the underlying cause. In the vast majority of cases, a second operation becomes necessary.

TREATMENT OF GASTROCOLIC OR JEJUNOCOLIC FISTULA

In these cases, treatment is surgical.

SUMMARY

1. An effort has been made to indicate the close relationship that must exist between surgeon and internist in determining the indications for operation upon the stomach.

2. The attempt has also been made to emphasize that whereas the method to be pursued must be left to the judgment of the surgeon, different conditions may require different methods. No one method is to be preferred in all cases above other methods.

3. In gastric surgery more than in any other branch of surgery, the internist should participate in the postoperative management of the patient, cooperating with the surgeon in postoperative treatment and guiding the patient's diet even during his stay in the hospital. In this way many of the complications and later sequelae of gastric surgery may be prevented.

4. It has been emphasized that many of the sequelae of gastric surgery, irrespective of the type of operation, such as atony of the stomach, spasm of the stoma, catarrh of the small and large intes-

tines, simulating recurrence of the ulcer or some surgical disease of the stomach, will yield to medical care.

5. If the attention of the internist to postoperative dietetic regimens is as strict as that of the surgeon to asepsis many recurrences of ulcer will be avoided.

REFERENCES

- ¹ HELD, I. W., AND GOLDBLOOM, A. ALLEN: "Fundamental Principles Governing the Clinical Interpretation of Hematologic Diseases," *M.Clin.North America*, 12:713-780, 1928.
- ² BILLROTH, T.: "Ein Beitrag zu den Operationen am Magen. Gastroraphie," *Wien.med.Wchnschr.*, 27:913, 1877.
- ³ WÖLFLE, ANTON: "Gastro-Enterostomie," *Zentralbl.f.Chir.*, 8:705-708, 1881.
- ⁴ PATERSON, HERBERT J.: "The Operation of Gastrojejunostomy and the Principles Which Should Determine Its Use," *Surg.,Gynce.& Obst.*, 18:423-428, 1914.
- ⁵ CANNON, W. B.: "Mechanical Factors of Digestion," E. Arnold, London, 1911.
- ⁶ CANNON, W. B., AND BLAKE, J. B.: "Gastro-enterostomy and Pyloroplasty," *Ann.Surg.*, 41:686-711, 1905.
- ⁷ VON EISELSBERG, A.: "Ueber die Magenresektionen und gastro-enterostomien," *Arch.f.klin.Chir.*, 39:785-840, 1889.
- ⁸ BEGG, A. A.: "The Influence of Gastro-enterostomy on Gastric and Duodenal Ulcers," *J.A.M.A.* 60:881-884, 1913.
- ⁹ BALFOUR, D. C.: "Series of Gastric Cases Treated by Excision," *Surg.,Gynce.& Obst.*, 24:731, 1917.
- ¹⁰ KOCHER, T.: "Ueber eine neue methode der Magenresektion mit nachfolgender gastro-duodenostomie," *Arch.f.klin.Chir.*, 42:542, 1891.
- ¹¹ POLYA, E.: "Zur Stumpfversorgung nach Magenresektion," *Zentralbl.f.Chir.*, 38:892, 1911.
- ¹² FINNEY, J. M. T.: "A New Method of Pyloroplasty," *Tr.Am.S.A.*, 20:165, 1902.
Ibid., "A New Method of Gastro-duodenostomy, End-to-side," *Tr.South.S.A.*, 36:576, 1923.
- ¹³ BEGG, A. A.: "Surgical Treatment of Gastric and Duodenal Ulcers; Affections of the Stomach," Burrill B. Crohn-W. B. Saunders & Co., 1927.
- ¹⁴ LAHEY, FRANK H.: "The Selection of the Operative Procedure for Various Gastric and Duodenal Lesions," *Surg.Clin.North America*, 13:541-561, 1933.
- ¹⁵ MARCHAND, F.: "Der Prozess der Wundheilung mit Einschluss der Transplantation," *Deutsche Ztschr.f.Chir.*, 61:599, 1901.
- ¹⁶ PRIEBRAM, B. O.: "Proteintherapie und chirurgische Therapie des Magen-und Duodenalgeschwurs," *Deutsche med.Wchnschr.*, 51:141, 1925.
- ¹⁷ FORGES, O.: "Bemerkungen zu 'jejunitis' von Rehder," *Deutsches. Arch.f.klin. Med.*, 173:330-331, 1932.
- ¹⁸ CARMAN, RUSSELL D.: "Roentgen Diagnosis of Disease of the Alimentary Canal," W. B. Saunders & Co., pp. 384-411, 1920.
- ¹⁹ MAYO, W. J.: "Chronic Ulcers of the Stomach and Duodenum," *Ann.Surg.*, 60:220, 1914.

- ²⁰ MOYNIHAN, SIR BERKELEY: "Abdominal Operation," Ed. 4, 1:292, W. B. Saunders & Co., 1926.
- ²¹ STRAUSS, HERMANS: "Fat Stools as Symptoms of Gastro colic Fistula," *Berl. klin. Wochenschr.*, 58:601, 1921.
- ²² WILBUR, D. L., AND EUSTERMAN, G. B.: "Probable Nutritional Night Blindness; Report of a Case," *Proc. Staff Meet., Mayo Clin.*, 8:457-461, 1933.
- ²³ CHLUMSKI, V.: "Ueber die Gastroenterostomie," *Beitr.z.klin.Chir.*, 20:231, 1898.
- ²⁴ DIBOLD, H.: "Über Ernährungsstörungen nach Magenresektion," *Med.Klin.*, 29:1138-1143, 1933.
- ²⁵ CONNER, H. M., AND BIRKELAND, I. W.: "Coexistence of Pernicious Anemia and Carcinoma of Stomach," *Proc. Staff Meet., Mayo Clin.*, 8:291-293, 1933.
- ²⁶ COLLENS, WILLIAM S., AND BOAS, LOUIS C.: "Absorption of Dextrose by Rectum," *Arch.Int.Med.*, 52:317-325, 1933.
- ²⁷ BAND, D., AND HALL, I. S., "Post-operative Massive Collapse of Lung; Clinical and Experimental Study," *Brit.J.Surg.*, 19:387-409, 1932.
- ²⁸ HELD, I. W., AND GOLDBLOOM, A. ALLEN: "The Treatment of Peptic Ulcer," *Canad.M.A.J.*, 24:372-383, 1931.

THE MEDICAL AND SURGICAL ASPECTS OF PEPTIC ULCER

By WILLIAM FRANCIS RIENHOFF, Jr., M.D.

Associate in Surgery, Johns Hopkins University School of Medicine; Assistant
Visiting Surgeon, Johns Hopkins Hospital, Baltimore, Maryland.

and BENJAMIN M. BAKER, Jr., M.D.

Instructor in Medicine, Johns Hopkins University School of Medicine; Assistant
Visiting Physician, Johns Hopkins Hospital, Baltimore, Maryland

Medical Aspects

INTRODUCTION

WHEN a patient comes to a physician complaining of symptoms which suggest peptic ulcer a number of important questions must be considered. First of all, the physician must decide as conclusively as he can whether or not the patient really has an ulcer. Assuming that he concludes after a diligent and thorough examination that an ulcer is present he must devise a plan of treatment suited to the particular needs of the patient. Finally, the patient must be told just what results he has the right to anticipate if he follows faithfully the plan the physician proposes. It is the purpose of this discussion to comment briefly upon the confused state of our knowledge of these fundamental problems. Medical writing upon the subject of peptic ulcer abounds in such conflicting opinions that the average physician is in a quandary when he is confronted with the concrete problem. One author reports the ease with which uniformly correct diagnoses are made by relatively simple procedures. Another points out the fallacy of attempting to separate patients with organic lesions from those who suffer from "functional dyspepsia". An exponent of one dietary scheme proclaims the superiority of his method of treatment and belittles other much used and successful methods. A medical man reports almost perfect success in a large group of cases treated by diets and drugs. A surgeon, analysing the results of medical treatment for comparison with his surgical results, inclines to boost unjustly the percentage of medical failures. There is end-

less contention over the relative merits of medical and surgical treatment, and a lack of uniformity of opinion as to the proper therapeutic steps one should follow. Finally, there is much confusion concerning prognostic predictions. It is, therefore, not remarkable that many physicians approach the problem of ulcer somewhat bewildered and skeptical with regard to its accurate solution. Familiarity with the inherent complexity of the ulcer problem is essential to an appreciation of the difficulty it presents both in diagnosis and treatment. The etiology of peptic ulcer is unknown. In spite of abundant experimental study, ulcers comparable to those encountered clinically, cannot be reproduced with regularity. Focal infections, gastric hypersecretion and hypermotility, deficient blood supply to the stomach and duodenum and a certain predisposing constitutional type have all been widely incriminated. While each may play a provocative or contributory role there is no incontrovertible evidence to prove that any one is uniformly or indeed ever alone the cause of peptic ulcer.

DIAGNOSIS

In the absence then of any clear cut etiological agent known to cause peptic ulcer, its diagnosis lacks a sure footing. There is no infallible test with which the diagnosis of peptic ulcer may uniformly be made. When tubercle bacilli are recovered from the sputum it is quite clear that tuberculosis is present. Physical examination of the larynx and lungs usually at once discloses quite clearly the nature and seat of the tuberculous lesion responsible for them. But such is not the case with peptic ulcer. The occurrence of haematemesis or the presence in a roentgenogram of a filling defect at the duodenal cap, while strong presumptive evidence of ulcer are not conclusive signs.

If one excludes hemorrhage and perforation there is a group of rather commonplace symptoms which usually leads the physician to suspect that his patient may have an ulcer of the stomach or duodenum. These symptoms are pain or heaviness in the epigastrium, sour eructation, heartburn, vomiting and constipation. The abdominal discomfort, which varies widely in intensity with the individual's susceptibility to pain, is usually related to the taking of food. In gastric ulcer the pain characteristically appears soon after

food is eaten; in duodenal ulcer it is usually separated from the taking of food by several hours so that night pain is often a feature of the symptomatology. In both gastric and duodenal ulcer the pain is usually relieved by taking food. Vomiting and eructation so regularly afford relief that sufferers often purposely bring them on. The severity of these symptoms goes frequently in cycles. For months at a time a patient may have them almost constantly and then without apparent reason they may disappear. These periods of remission vary from weeks to months and even to years. Relapses tend to occur in either the Spring or Autumn.

That this group of symptoms in patients with peptic ulcer depends upon gastric hypersecretion of acid chyme, together with hypermotility and spasticity of the alimentary tract, is now generally accepted. Unfortunately, however, hyperacidity and hypermotility are not confined to stomachs which are ulcerated. An appreciable number of normal persons who do not have and never develop peptic ulcer, have gastric hyperacidity and hypermotility. Of still greater importance is the fact that a very large group of "dyspeptic" patients with gastric hyperacidity and hypermotility complain of symptoms varying from a little heartburn and constipation to the group constituting the typical "ulcer syndrome". A few of these patients develop ulcer, but most of them never exhibit any definite anatomical lesion which may be held responsible for their symptoms. Not infrequently the chronicity of these "functional" symptoms and their resistance to medical treatment bring these patients to operation. For obvious reasons they are no better after operation than they were before, indeed they are often worse. If then identical symptoms occasioned by gastric hyperacidity, hypermotility and spasticity, may be present in patients without as well as with ulcer, what data justify the diagnosis of ulcer?

Perforation at once establishes the diagnosis and needs no further comment. Hemorrhage is an exceedingly important manifestation. An appreciable haematemesis is said to occur at some time during the course of 50 per cent. of all ulcers of the stomach. Provided then that hemorrhage from oesophageal varices, trauma and corrosive irritants is excluded, haematemesis is diagnostic of an ulcerative lesion in the stomach and these ulcerative lesions are much more frequently peptic ulcers than carcinomata. Blood in the

stool while a valuable sign is more difficult to interpret than haematemesis. The possibilities are much more numerous and many of them difficult to exclude. Ulcerative lesions in the rectum and lower bowel are readily detected by simple manual or proctoscopic examination. As haematemesis is the strongest evidence of a gastric ulcer, so a large tarry stool is presumptive evidence of ulcer of the duodenum. Slow seepage of blood into the stool is, however, more frequent in cancer of the stomach or bowel than in ulcer. Other measures of differentiation must then be employed.

In the early days of gastro-intestinal roentgenology it was thought that at last an infallible method of detecting peptic ulcer had been discovered. Experience has shown, however, that this expectation has not been fulfilled. The roentgen ray is admittedly the most valuable method of diagnosis but it is not infallible. Its disclosures are of value only when they are interpreted by an experienced roentgenologist. A large crater-like "niche" may be apparent even to an inexperienced observer, but the differentiation of filling defects due to ulcer from those due to spasm can be made only by the trained eye. Another possible source of error is the fact that ulcers in the posterior wall of the pylorus are clearly disclosed only rarely by the roentgen ray. Filling defects in the stomach or duodenum are of value in the diagnosis of ulcer only when they are constant and when in doubtful cases atropine has been given to eliminate the possibility that they may be due to spasm. A single examination in a questionable case is of little value.

Pyloric obstruction is more often due to cancer than to peptic ulcer. Fortunately, however, by the time cancer has obstructed the pylorus there is rarely any longer doubt about the diagnosis. True pyloric obstruction is exceedingly rare in functional spasticity and when present is never constant. Therefore, if cancer can be excluded, the presence of characteristic signs of pyloric obstruction, namely obstructive phenomena in the gastric contents, epigastric peristaltic waves in a distended stomach and the retention of a meal opaque to the roentgen ray are almost certain evidence of the presence of a peptic ulcer.

The difficulty of diagnosis is therefore very real. The young and inexperienced physician usually receives a depressing blow to his diagnostic pride early in his experience with patients having diges-

tive disorders. A patient comes to him and tells a story of chronic "dyspepsia". He complains of heartburn coming on two hours after meals which is relieved by soda and food; of constipation; of occasional nausea and vomiting, the vomiting relieving the pain. A test meal reveals an abundant highly acid gastric secretion. A single test for occult blood in the stool is positive but the patient has not been on a meat free diet. An examination under the fluoroscope reveals irregular filling of the duodenal cap by the opaque meal. The clinical picture of peptic ulcer is apparently complete. A well planned dietary and medicinal regimen gives the patient little or no relief and operation is undertaken because both physician and patient are disheartened. Under these circumstances the physician will be surprised and embarrassed when at operation, as often happens, no ulcer is found. Such an hypothetical case is not infrequently an actual occurrence. Experiences such as these teach the importance of conservatism in diagnosis and the necessity of repeated and careful roentgen ray studies and examinations of the stools for blood. Ulcers may be present and yet the roentgen rays not show them and blood be absent from the stools; nevertheless, these two methods of examination are the safest with which to avoid diagnostic errors.

MEDICAL TREATMENT

It is fortunate that the medical treatment of peptic ulcer and of the functional syndrome which simulates ulcer is much the same. Although this fact is true it is no just excuse for slovenly clinical study; still it may hide some of our diagnostic errors. Without considering at the moment the merits and demerits of medical and surgical treatment, nor the indications and contraindications for their use, it is a fact that most patients thought to have peptic ulcer are at first treated medically. Medical treatment as we shall see gives far from perfect results. It does, however, afford many patients adequate relief and shields them at least temporarily from the slight though definite risk of a major operation.

The fundamental precept of treatment is to remove the cause when possible and to repair what damage has been done. The uncertainty of our knowledge of the etiology of peptic ulcer has already been commented upon. Any therapy directed to removing the cause must therefore be empirical. We can do little to alter a constitu-

tional tendency toward gastric hypersecretion and hypermotility though we may lessen for a time the intensity of nervous impulses which enhance them. Though undoubtedly not solely casual, focal infections, particularly those in the appendix and gall bladder, do much to retard the healing of an ulcer or to reactivate it from a quiescent state. All focal infections should then be judiciously evaluated and properly treated when possible by eradication.

The principle underlying the repair of damage done is rest to the ulcer bearing area. By rest is meant not only physical but mental rest. Patients with peptic ulcer frequently present an extremely difficult mental attitude. Many of them have been ill for a long time and have become discouraged and disheartened by the repeated failures of treatment. They are emaciated and weakened not so much from an aversion to food as from fear of the consequences of eating it. They are commonly constitutional pessimists; constant heartburn, sour eructation, nausea, vomiting, constipation and sleeplessness all exaggerate their mental distress. The naturally resulting nervous disturbances make things even worse by affecting deleteriously the motor and secretory functions of the stomach. Proper medical care must then be directed not only toward obtaining rest for the stomach but what is equally important toward securing mental repose. Whenever possible a rest cure in a hospital is the most effective means of accomplishing this desired result. Should this impose too great a financial strain then the purpose for which it was proposed is defeated and the ambulatory method of treatment must then be tried. The physician must put himself in the place of the patient and relieve him of the additional worry of making his own decisions.

Diet and drugs one attempts to maintain or replace lost without mechanically irritating the ulcer and to reduce secretion, spasticity and constipation. These fundamental principles underlie all of the many schemata that have been employed. Experience teaches us that one possesses relatively little advantage over another. It would serve no useful purpose to review the many medicinal and diet routines that are used. Any modern textbook of medicine may be consulted. The most widely used in this country is that devised by Sippy. In very acute cases and particularly when there is bleeding, a preliminary period of starvation is

desirable and when feeding is begun it must be given cautiously with careful observation to be sure bleeding does not return. Greatly emaciated patients require diets of high caloric value while well nourished patients may profitably forego large quantities of food and thus reap the benefits of more rest to the stomach. A patient with pronounced hypersecretion and hyperacidity needs more alkali to control his symptoms than one with relatively little acid secretion. Whatever schema of diet and alkali administration is followed, provided it conforms approximately to those tested by experience, the results will in all probability be the same. It will need to be varied both in quality and quantity for each separate patient. A plan which fulfills perfectly the needs of one patient may be unsuitable for another.

We may summarize the principles of medical treatment as follows: Mental and physical rest are essential. The ulcer must be protected from irritation by as bland a diet as can be given. The diet must be varied quantitatively and qualitatively to meet the needs of each patient. Hyperacidity must be reduced sufficiently by alkalis to allay the symptoms it provokes. Spasm must be controlled by the use of belladonna in amounts that are tested to the point of each patient's tolerance. Measures supplementary to the effect those just enumerated will possess, must be directed toward the relief of constipation. These are all widely known methods of treatment and the success of one physician as compared with the failure of another does not depend upon any subtle touch in the use of such simple methods. Success depends upon proper diagnosis and selection of cases suitable for medical treatment; upon an appraisal of the length of time a given patient should follow a rigid regimen; upon an ability to make a patient continue temperance in eating, smoking and drinking, and in the preservation of his physical and emotional reserve. A rigid ulcer cure eminently successful will of course fail when followed by debauches of eating and drinking. On the other hand, continuous dieting and taking of drugs according to a rigid schedule may develop "gastric neurosis" and though cured of ulcer the patient may be worse than before. A middle ground between these two hypothetical extremes will give the best success in the medical treatment of peptic ulcer.

RESULTS OF MEDICAL TREATMENT

The successful physician must always be ready with prognostic facts. Intelligent patients demand this information and particularly those with peptic ulcer. Many of them have previously experienced unsatisfactory therapeutic results. Those whose illness is recent are likely to be familiar with the usual chronicity of ulcer symptoms. Reliable prognostic information then is necessary not only to meet the demands of an inquisitive patient but in order that therapeutic measures may be soundly adjusted to the individual problem of each patient.

There are few medical conditions in which prognostic acumen is more difficult to apply than in peptic ulcer. The situation is very much as it was with tuberculosis of the lungs thirty years ago. Then, patients with the most trivial and insignificant pulmonary signs were hurried off to sanatoriums to be cured of their tuberculosis. Many of course never had tuberculosis and the percentage of cures was exceedingly high. Now with more exact knowledge of the disease the results of treatment are not nearly so brilliant as they once were.

A study of the literature reveals a most distressing diversity of opinion about the results of treating medically patients with peptic ulcer. That ulcers often do heal at least to the point where it is unlikely that they will give further symptoms is established by the disclosures of autopsy. On the other hand, the problem clinically is exceedingly difficult. No one doubts that cases treated medically with the most meticulous care may obtain little or no relief whatever from their symptoms. One therefore accepts with skepticism reports of almost perfect success in a large series of cases. Certainly it is unlikely that such success is possible and these series undoubtedly contain cases whose symptoms arose from conditions other than ulcer. The problem is almost hopelessly complicated by the inherent complexities already discussed. In this complexity the difficulty of diagnosis plays the major rôle. Such other factors as age of the patients, the duration of symptoms, the occurrence of hemorrhage, the selection of cases, the ability of the patients to adhere to reasonably satisfactory medical routines and the interpretation of results by different observers all materially affect the reliability of the available information.

There are few satisfactory sources in the literature from which such desired information can be obtained. An attempt has been made, however, to collect certain data from reports of cases apparently carefully diagnosed, unselected and followed for a reasonably long period of time. It is agreed that so far as immediate results are concerned, from 85 to 95 per cent. of patients whose symptoms have antedated the institution of medical treatment by no longer than a year are completely relieved. As the duration of preexisting symptoms increases, however, the results are more and more unfavorable. In Neilsen's large series only 40 per cent. of the patients whose symptoms antedated the institution of treatment by ten years or more obtained immediate relief. Twenty-five per cent. were improved and 35 per cent. were complete failures. One may therefore conclude that the probability of complete immediate relief in the medical treatment of peptic ulcer is inversely proportional to the duration of symptoms prior to the institution of medical measures.

As regards the permanence of relief, the situation is vastly different though somewhat dependent upon similar factors. After a lapse of five years 50 per cent. of patients immediately relieved have experienced one or more recurrences of their symptoms and after ten years this figure has risen to 75 per cent. Neilsen followed a large series of cases from two to twenty years. Seventy-seven per cent. of those whose symptoms had existed only six months derived good permanent results. Seventy-five per cent. of those whose symptoms had preceded treatment by as long as ten years obtained poor end results. In 262 of his cases, 88 per cent. of recurrences occurred within the first two years.

Surgical Aspects

A present day discussion of the diagnosis of peptic ulcer leaves one perplexed and bewildered. Physicians carefully analyze the signs and symptoms of the disease and before making a diagnosis call to their aid all pertinent laboratory procedures. The roentgenologist has fully explained the significance of the "niche" due to muscle spasm, the "notch" on the lesser curvature and the "deformity" of the duodenal cap. However, in spite of all this knowledge and the care used in interpreting it the diagnosis of peptic ulcer remains difficult and is often uncertain. Faith is a great

theological virtue for we are told "blessed is he that hath not seen and yet hath believed", but it is not wise for the surgeon to transfer this simple, praiseworthy trust to the diagnosis of peptic ulcer, lest he may often experience the chagrin and embarrassment of opening the abdomen and finding no ulcer.

In discussing the treatment of chronic peptic ulcer we find an equally great difference of opinion. However, it is agreed upon that medical treatment should precede surgical treatment. It has been proved again and again at autopsy and at operation that chronic peptic ulcers do sometimes heal and often permanently. Therefore this natural tendency to repair should be given an opportunity to heal the ulcer before surgery is called on to assist. Much will depend upon the particular patient, his stability or lability, and much also upon his social and economic position. Furthermore, the length of time necessary for an ulcer to heal must be taken into account. This will vary according to the size, shape and consistency of the ulcer. Foreign authors consider that the time required for healing is longer than do many American authors. For example Moynihan says: "The longest period occupied in the healing was three years and nine months. An ulcer the size of a shilling requires a period of about six weeks for firm cicatrization." A period of three weeks stated by some to be adequate is, in his opinion, far too short. "Such claims do not receive the slightest support from my much larger series."

It is unfortunate for both patient and doctor that often a few days of complete mental and physical rest together with a carefully regulated diet rapidly relieve the symptoms of peptic ulcer. The patient then becomes rebellious and weary of the treatment long before the ulcer could possibly have healed satisfactorily. Again the natural remissions and exacerbations of the disease are apt to contribute further to the difficulty of treating the patient with ulcer. And finally inadequate medical treatment is not only ineffective in permanently relieving symptoms but also it increases the probability of dangerous hemorrhage, of perforation, and of malignant change in the ulcer. Furthermore, it often ends the patient's unhappy and uncomfortable existence if the disease is allowed to run its natural course without adequate medical treatment. The shortest time that one should expect for a healing of a chronic peptic ulcer is two

months after all clinical signs and symptoms have disappeared and during this period the patient's activities should be greatly restricted. Periods short of this are more often than not insufficient and therefore the results are unsatisfactory. This fact alone dooms to failure a great many patients who because of their economic and social position are unable or unwilling to submit to what is actually adequate medical care. In such instances medical treatment is handicapped and at an unfair disadvantage. The vast majority of patients with chronic peptic ulcer never give medical treatment a fair trial.

INDICATIONS FOR SURGICAL TREATMENT

Some form of operation is indicated in the treatment of chronic peptic ulcer under the following circumstances:

A. *Imperative Indications.*

1. In the event of acute or chronic perforation of the ulcer.
2. To relieve mechanical obstruction either at the pylorus or from hour-glass contraction of the stomach.

B. *Probable Indications.*

1. In the event of continued hemorrhage.
2. When, in spite of adequate medical treatment, the patient's symptoms continue.
3. When the patient is unable because of social or economic restrictions to carry out proper medical treatment.
4. To avoid the occurrence of malignant change in a chronic ulcer.

A-1. *Perforation.*—It is self-evident that immediate operation is necessary for acute perforation of a peptic ulcer. It is likely to prevent a formidable abdominal catastrophe and prove to be a life-saving measure. Undoubtedly the fact that the great majority of patients with a perforated ulcer are found on the public rather than the private wards indicates that chronic peptic ulcer inadequately treated is fraught with the danger of continued and progressive ulceration. The private patient has access to more intelligent and skillful medical care and, furthermore, is better able to take advantage of relatively long physical and mental rest coupled with the proper dietary restrictions and regulations. The greater incidence

of acute perforation of chronic peptic ulcer in the poorer class of patients is certainly a pertinent commentary on the inadvisability of ambulatory treatment of so-called "chronic dyspepsia." This unwelcome fact cannot be entirely blamed upon inaccuracies in diagnosis and treatment, for many patients are unwilling from gross ignorance or are unable from poverty to follow the physician's advice. When the diagnosis of acute perforation of a chronic ulcer of the stomach or duodenum has been made, the patient should be operated upon immediately, for the mortality is in direct proportion to the number of hours elapsing between the onset of the acute symptoms of perforation and the operation.

In many patients we encounter the symptoms and signs of a subacute or chronic perforation. In such cases there is, as a rule, increase in the severity of the pain. Its characteristic periodicity tends to disappear, it becomes continuous and tenderness on palpation develops. A slight daily elevation of the temperature is associated with an increase in the leucocyte count. Not uncommonly roentgenograms reveal a progressive ulceration of the stomach or duodenal wall. In this type of case operation should be performed as soon as possible. One cannot predict with safety how long this progressive ulceration will go on before complete perforation occurs. Patients who survive operations for a perforated ulcer, even though nothing more is done at operation than simple closure of the perforation, have often obtained permanent relief from their symptoms. This fact strongly suggests that the mere excision of an ulcer is the simplest and best of all operative procedures. It is, of course, not always possible merely to excise the ulcer, but this will be later discussed in greater detail.

A-2. Mechanical Obstruction.—Undoubtedly chronic gastric and duodenal ulcers begin as acute ulcerations which for some unknown reason do not heal spontaneously. Nevertheless, chronic ulcers do heal either spontaneously or as a result of medical treatment and in so doing often cause cicatrization of portions of the stomach or duodenum which require correction by operation. Pyloric obstruction is by far the commonest effect of such healing and is more often than not caused by duodenal stenosis due to healing of a duodenal ulcer. The less common variety of obstruction of the stomach is the so-called "hour-glass" constriction due to healing of

an ulcer in the body of the stomach. Although occasionally slight temporary improvement may be obtained by the medical treatment of obstruction no more brilliant surgical results are ever seen than those which follow the relief of pyloric obstruction by gastro-enterostomy or some form of plastic operation for hour-glass contracture of the stomach. Patients, who for years have been emaciated and confirmed digestive invalids, vomiting stagnant and fermented stomach contents, existing in a weakened and unhappy state on a restricted diet are often restored to vigorous health by a gastro-enterostomy. For pyloric or duodenal stenosis any form of gastro-enterostomy suffices, either gastro-duodenostomy or gastro-jejunos-tomy.

B-1. *Hemorrhage*.—Although hemorrhage is rarely fatal, it is one of the most frequent and serious complications of chronic peptic ulcer. This complication is one which requires close cooperation between patient, physician and surgeon. The extent of bleeding, which may vary from a sudden massive hemorrhage to a little oozing shown by occult blood in the stool, will determine whether the treatment is to be surgical or medical. Generally speaking, during the active bleeding period the patient should be treated medically until the circulatory balance has been reestablished. Fortunately, the majority of patients who have a massive hemorrhage recover under this form of treatment. However, there should always be a surgeon in consultation, so that he may observe the clinical course of the case from the beginning and not be called in when the patient is moribund from exsanguination. In spite of this general rule, however, there are occasional patients, fortunately very few, who have suffered very little from the symptoms of ulcer but who previously have had one or more large hemorrhages. The clinical features of severe hemorrhage overshadow the usual symptoms of chronic peptic ulcer. Often under observation the bleeding continues with more or less intensity and the anemia progresses in spite of complete bed rest, nothing by mouth, and repeated small transfusions of blood. It is unwise to temporize under these circumstances; the patient should be operated upon at once. A massive transfusion should be given both before and after operation and salt and glucose should be administered by vein during the whole course of the operation. In the great majority of these cases the bleeding point will be found at the

base of an indurated ulcer on the posterior wall of the first portion of the duodenum. The gastro-duodenal or pancreatoduodenal artery is usually the vessel eroded and because of the excessive fibrosis of the floor of the ulcer the lips of the mouth of the vessel are held open and cannot fall together. The clinical features of this type of bleeding are rather characteristic. There is a history of sudden massive hemorrhage, or perhaps several, with copious haematemesis or tarry stools or both. The patient feels dizzy and weak at the time of bleeding and may even collapse. The usual symptoms of chronic peptic ulcer are relatively insignificant or totally absent. As a rule, the bleeding is unremitting while the patient is under observation in the hospital. The type of very actively eroding ulcer causing the bleeding is the analogue of the anterior wall perforating ulcer. It is really a posterior perforation into the pancreas. The patient should be observed only long enough to be certain of the progressive loss of blood and should then be operated upon and treated as he would be for hemorrhage from anywhere else in the body. The operation should stop the bleeding and nothing further should be attempted. These patients, needless to say, are severely shocked and therefore poor operative risks. The duodenum should be opened in its first part, the ulcer exposed and the bleeding point transfixed. If this cannot be done, the gastro-duodenal artery should be tied above the duodenum. The cases of this type which have come to autopsy have revealed the fact that a thrombus cannot form in the mouth of the eroded vessel until bleeding causes the blood pressure to fall and remain very low. But as soon as the blood pressure becomes elevated the mouth of the vessel is reopened and another loss of blood occurs. For this reason any treatment short of closing the aperture in the vessel or ligating it is foredoomed to failure. This type of bleeding peptic ulcer is practically the only one in which there is grave danger of death from hemorrhage unless surgical measures are immediately employed, therefore it has been discussed in some detail. Other types of bleeding from peptic ulcer are much less grave. However, although rarely fatal, nevertheless they constitute a constant menace to the health and happiness of the patient. It has been shown most convincingly by Jordan and Kieffer of the Lahey Clinic, that hemorrhage, particularly repeated hemorrhage, is of considerable prognostic significance in estimating the

probability of failure of medical treatment. Of the cases treated medically, a history of two or more hemorrhages was obtained in only 1.6 per cent. of the successful, but in 46 per cent. of the unsuccessful cases. It is the general opinion, therefore, that persistent or repeated hemorrhage indicates continued activity of the ulcerative process and should be treated by operation. A single hemorrhage of moderate severity is insufficient ground for advising an operation, if the patient has remained in good general condition. It is, of course, most confusing when, in the absence of any clinical or roentgenological evidence of ulcer, a hemorrhage occurs. In these rare cases inflammatory lesions in the duodenum of insufficient size or consequence to give clinical evidence of their presence are thought by Balfour to be responsible. In his experience persistence of bleeding is usually followed by the development of positive roentgenological evidence of ulcer. Other possible sources of hemorrhage should always be kept in mind when operating for a bleeding peptic ulcer. The operative treatment of chronic bleeding ulcer will be included in the general consideration of operative technique.

B-2. *Medical Failures.*—Occasionally in spite of adequate medical treatment the symptoms of peptic ulcer persist. The peace of mind, health and happiness of the patient are destroyed. The fact that perfect cooperation on the part of the patient to a wise and adequate regimen is insufficient to bring about even a disappearance of symptoms, to say nothing of complete healing of the ulcer, makes success of further medical efforts extremely improbable. The majority of patients who die of chronic peptic ulcer or its complications do so either because adequate medical treatment has failed or because the patient has not followed sound medical advice. Death in these cases is the result of long continued activity of the ulcer which results in perforation, hemorrhage, or inanition combined with secondary anaemia. Persistence in insufficient medical treatment has been proved to be not only of little value but also highly dangerous. Even if one excludes the possibility of malignant degeneration of a benign ulcer, medical treatment of ulcer undoubtedly has a higher mortality rate than has conservative operation. Therefore, when medical treatment has failed surgical treatment should follow without delay. Not only are the immediate and late mortality rates lower but the end results are more satisfactory. It is unfair

to subject a patient to the danger incident to continued activity of an ulcer or to condemn him to a state of invalidism without allowing him the advantages which surgery offers.

B-3.—The discussion in the preceding paragraph applies equally well to the group of patients who are socially and economically unable or else unwilling for various reasons to follow faithfully medical treatment. The great majority of dispensary, semi-private and poor patients fall into this group. It is also this group that contains the majority of patients suffering from chronic peptic ulcer. Medical treatment for them is an injunction of almost unattainable perfection. The problem is not so much a medical one as a problem in social economics. To have the best chance the patient should have rest in bed, freedom from anxiety, careful supervision of diet and complete repose. To-day very few people indeed can meet these requirements. Therefore, for this large group of patients having chronic peptic ulcer operation is much superior to medical treatment.

B-4.—It has not yet been proved beyond question that a benign peptic ulcer ever becomes malignant. Indeed it is more likely that chronic ulcers which are found to be malignant have been so from the beginning. It may be clinically impossible to distinguish them in the early stages from benign ulcers; it may not always be possible to differentiate them by their gross appearance and even difficult to diagnose them microscopically. However, in the majority of instances clinical data together with the gross findings at operation serve to differentiate carcinoma of the stomach from benign ulcer. During the past twenty years opinion has changed from the extreme view once held that 75 per cent. of chronic benign ulcers of the stomach undergo malignant change. It is now felt by many that 5 to 10 per cent. is a more accurate figure. There are a few, with whom we agree, who are of the opinion that an ulcer is either malignant from the beginning or else does not become malignant.

OPERATIVE PROCEDURE

A detailed discussion of the relative merits of the many different operations which a versatile surgeon should be able to employ in his treatment of peptic ulcer would be as out of place in an article of this sort as would an exposition of the minute details of intestinal surgical technique. However, attention should be focused

on several fundamental facts concerning the choice of the operative procedure. The many operations that have been devised for the treatment of chronic peptic ulcer are evidence of the lack of unanimity of opinion in regard to the proper or ideal operation. The surgical treatment of ulcer like the medical treatment is largely empirical. The factors responsible for the occurrence and persistence of a chronic peptic ulcer are at present unknown. Therefore, it is not possible to attack directly by either surgical or medical measures the etiological agent or agents responsible for the formation of an ulcer. The disturbed physiological mechanism of the stomach associated with chronic peptic ulcer may have preceded or followed the actual ulceration; nevertheless, it must be taken into consideration when permanent relief from the symptoms of a chronic peptic ulcer is the anticipated goal. The effects of operation upon the motor and secretory functions of the stomach are little understood, and the rationale of the various operations is difficult to explain; nevertheless, it is known that certain procedures are successful in a high percentage of cases even though the complete reason for this success is not at present evident. In view of our present lack of knowledge not only of the immediate but also of the late effects of operations upon the stomach it seems logical to conclude that the simplest operation which gives the best possible results is the one which should be chosen. In the past an attempt has been made to differentiate operations suitable for relieving gastric ulcer from those suitable for duodenal ulcer. So far as can be proved there is no difference between these benign ulcerations except their anatomical site. The location of the ulcer may bring about some difference in the symptoms it produces and in the character of the complications and may call for the application of certain surgical procedures. However, it has never been demonstrated that gastric and duodenal ulcer differ in etiology, in pathology, or in response to surgical treatment. The only practical difference that need concern the operator in treating chronic duodenal and gastric ulcer is a mechanical one. The excision of a small ulcer on the lesser curvature of the stomach may be very easily and quickly done and require, because of the relatively large size of the viscus, no further plastic operation to reestablish the continuity of the gastro-intestinal canal. However, conditions are otherwise when a duodenal ulcer is excised. The relatively small size of the duodenum requires some type of

plastic operation to make up for the substance lost in removing the ulcer.

At present it may be said that there are two schools of practice among surgeons particularly interested in the treatment of chronic peptic ulcer. One school favors large resections of the stomach not only for gastric but also for duodenal ulcer; the other group favors less radical measures such as localized excision of the ulcer alone or this combined with some form of gastro-enterostomy. The justification for extensive resection of two-thirds or more of a patient's stomach for a small duodenal ulcer is not apparent. The operative mortality alone, to say nothing of the as yet unknown late effects, has made the sacrifice of large portions of an otherwise normal stomach seem unwarranted. The rationale of these radical procedures is not at all clear. If it is to reduce the high acidity then only the acid bearing area of the stomach should be removed. Roughly, this acid bearing area is confined to the fundus, approximately the middle of the stomach between the cardia and the pylorus. If this acid bearing area should be removed the procedure would be a sleeve resection of the middle portion of the stomach. The pylorus and pyloric antrum in these massive resections is unnecessarily sacrificed under the assumption that a hormone causing the acid secretion is eliminated. This of course is unnecessary if the acid bearing area has been removed. Experimentally and clinically we have found that the normal acid content of the stomach tends to recur in spite of extensive resections. It is not possible clearly to delimit the acid bearing area which is subject to individual variation. Therefore how can one be certain of accomplishing an exsection of the acid bearing area? If one cannot be certain of this then such a radical resection is unjustified. In animals as well as in human beings in whom part of the fundus or acid bearing area has been left, after some months the acid secretion reapproximates its pre-operative level. Incomplete ablation of the acid bearing area does the patient no good whereas it increases the operative risk and wastes valuable stomach tissue. A further consideration of importance is that marginal ulcers occur not infrequently following resections of the stomach. Extensive removal of a large portion of the stomach is a difficult operation to perform and it constitutes a danger to the life of the patient even in the hands of those particularly skilled in gastric surgery. It would certainly be unwise to recommend to the

average surgeon an operation fraught with great danger, particularly since there are more conservative methods equally efficacious and yet attended with a much lower death rate.

Unquestionably simple excision of the ulcer when feasible is the procedure of choice. This operation combines minimal mortality with excellent immediate and late results. It may well be said of the surgery of peptic ulcer that the simpler the operation the better the result. Local excision of the lesion alone is usually possible only when the ulcer is located on the anterior wall of the lesser or greater curvatures of the stomach and but rarely when situated on the posterior wall. As a rule only relatively small ulcers can be treated by excision. The postoperative course of patients who have had a small ulcer excised is usually uneventful. Furthermore, both the immediate and remote results are excellent and the formation of marginal ulcers is uncommon. In view of the success of simple excision this operation is undoubtedly preferable to more radical procedures such as gastro-enterostomy or resection of the stomach. When simple excision is not contraindicated it removes the ulcer with the least possible trauma to the stomach. In some cases, however, it is not possible to excise the ulcer without at the same time resorting to some form of plastic operation in order to preserve the continuity of the gastro-intestinal tract. In many other cases excision is not feasible. It is then that some form of gastro-enterostomy is the operation of choice. Gastro-jejunostomy when properly performed is unquestionably the most successful of all operations of this class for the surgical relief of chronic peptic ulcer. It is an operation which has become fairly standardized and is probably the most generally useful of all operations upon the stomach. Furthermore, the relative simplicity of the operation is an important point in its favor. Operations for peptic ulcer must be safe as well as effective for only the occasional patient can afford to travel to some of the larger medical centers in order to be operated upon by a surgeon devoting himself entirely to gastric operations. From the standpoint of results, both immediate and late, gastro-jejunostomy is superior to more radical procedures. The results from many different clinics in the United States reported before the American Surgical Association in 1930 demonstrates: First, that the mortality following gastro-jejunostomy is less than 2 per cent.; the mortality from all other operations in the hands of specialists, is over 10

per cent. This mortality rate would undoubtedly soar if extensive resections of the stomach were practiced generally. Second, that more patients die following a radical operation, e.g., partial gastrectomy, than the total number of failures, including deaths and recurrences, following conservative methods like gastro-jejunostomy. Third, that in 85 per cent. to 90 per cent. of the cases of chronic peptic ulcer, cures were obtained by some form of gastro-enterostomy, namely, pyloroplasty, gastro-duodenostomy, or gastro-jejunostomy. Balfour reported that 79 per cent. of his patients with gastric ulcer were relieved and that in many the lesion has disappeared completely. This is a powerful argument against those who insist on resection of the stomach for gastric ulcer. It is the consensus of opinion of those particularly interested in the surgical treatment of peptic ulcer that conservative types of operation are preferable in duodenal ulcers and also in the great majority of gastric ulcers. If following a conservative operation the activity of the ulcer continues or a marginal ulcer develops, then radical resection may be advisable. Reports from various clinics state that the occurrence of marginal ulcers is about as frequent following partial gastrectomy as after gastro-enterostomy. This is not to be wondered at when one takes into consideration the fact that when resection is done the site of the anastomosis is usually located in the acid bearing portion of the stomach. Since free hydrochloric acid persists after extensive resections of the stomach it is likely that marginal ulcers will occur in some of the patients operated upon by this method. It is a very important consideration that if a conservative operation such as gastro-enterostomy fails to bring about healing of the ulcer or is followed by a marginal ulcer, then the gastro-enterostomy may be disengaged and some more radical operation performed. In the event that the primary ulcer heals and a marginal ulcer develops at the site of the anastomosis, the gastro-enterostomy may be closed. On the other hand, if the primary ulcer is not healed by the original gastro-enterostomy, the ulcer together with part of the stomach may be removed without disturbing the anastomosis. In this way the original gastro-enterostomy is converted into a Billroth 2 type of partial gastrectomy. This is much more easily performed than resection of a part of the gastric pouch remaining after a primary partial gastrectomy should a marginal ulcer later develop.

There are individual differences of opinion about the most useful type of gastro-enterostomy. Gastro-jejunostomy will be found a useful and effective operation in from 80 to 90 per cent. of the cases. This operation has stood the test of time having been employed certainly in a greater number of cases, over a longer period of years, and by a larger number of operators than any one other or perhaps all other operations combined. These facts compose an almost irrefutable argument in favor of the operation and there are few indeed who will not readily agree that for the cure of chronic peptic ulcer gastro-jejunostomy is unequalled. However, there are certain ulcers especially in younger patients, and also some of the severe hemorrhagic posterior duodenal ulcers, which are best treated by performing a pyloroplasty. In others, and this group is daily becoming larger, it is possible and preferable to use the lower portion of the duodenum and to do a gastro-duodenostomy. In other words it is obvious that *one and only one operation* will not give perfect results in all cases of chronic peptic ulcer, any more than one shoe will fit every foot. Especially is this true when one takes into account the fact that, as a rule, surgery is resorted to only when other methods of treatment have failed. Therefore, as stated at the beginning of this discussion the best results will be obtained when the surgeon, familiar with the various operations and their relative merits, selects the operation best suited to the particular patient. In making the selection it is certainly short sighted not to take into consideration the possible failure of the operation to accomplish its purpose. Therefore, performing a radical resection of the stomach at once before giving the patient an 80 per cent. or 90 per cent. chance of being cured by a conservative operation is playing the trump card first. It is common experience that failure after one form of gastro-enterostomy has been followed by success following a second. For instance, a failure following pyloroplasty may be transformed into a very successful result by a subsequent posterior gastro-jejunostomy, and a gastro-duodenostomy performed after the failure of a gastro-jejunostomy has often been followed by complete success. Radical resection of the stomach should unquestionably be reserved for those cases in which the more simple type of operation has proved ineffectual. It will be found that this group reserved for the more radical operation will be exceedingly small.

PURPURA HEMORRHAGICA (THROMBOCYTOPENIA)*

An Evaluation of Our Present Knowledge

By R. L. PAYNE, M.D., F.A.C.S.

Surgical Staff St. Vincent's and Norfolk Protestant Hospitals,
Norfolk, Virginia

and

By R. C. WHITEHEAD, M.D.

Medical Staff St. Vincent's and Norfolk Protestant Hospitals,
Norfolk, Virginia

IN CONSIDERING Purpura Hemorrhagica, the Essential Thrombopenic Purpura of Eppinger,¹ one cannot discuss the subject in the usual manner by giving a detailed description of its etiology, pathology, symptomatology, diagnosis and treatment; for very little is definitely known of the disease and the interrelation of the facts that have been developed by arduous investigation is by no means completely understood. The manner of onset and the symptomatology are well known and the differential diagnosis from other hemorrhagic conditions is well established, but the etiology is obscure and its treatment so far has been only partially successful in a small number of cases. Even among these the apparent cures are too few to establish beyond reasonable doubt the exact therapeutic worth of the measures employed. The cause of the disease, the manner in which its manifestation develops, its pathology and the surest methods of effecting a cure are rewards awaiting future work on the problem. The subject will therefore be considered in an informal way by taking up the facts which have been established and drawing from them the conclusions which seem to be logical. Approached in this manner the subject of Essential Thrombopenia, or Purpura Hemorrhagica of Werlhof, is an intriguing study.

Thrombocytopenia is a clinical picture, the presenting feature of which is hemorrhage into the skin, mucous membranes, submucous and subcutaneous tissues, and the characteristic symptom a fall or

* Presented by invitation before the Raleigh Academy of Medicine, Raleigh, North Carolina, November 18th, 1933.

lowering of the number of thrombocytes. Hemorrhage of this kind is not peculiar to the disease, but may appear in any one of a large group of other conditions and often occurs in infections and intoxications which bear no other resemblance to purpura hemorrhagica. When spontaneous bleeding is accompanied by a characteristic fall in the number of thrombocytes then only is the condition called thrombocytopenia. Confusion is apt to occur in the discussion of hemorrhagic diseases unless the fundamental and characteristic features of each are kept in mind.

In Osler and McCrae,² System of Medicine, Pratt gives the following classification of thrombocytopenia:

- (I) Essential thrombopenic purpura (Essential thrombopenia, Purpura hemorrhagica, Werlhof's disease).
- (II) Symptomatic thrombopenic purpura
 - (a) *Blood diseases.*
 - Leukemia
 - Agranulocytosis
 - Pernicious aplastic anemia
 - Hemolytic jaundice
 - Goucher's splenomegaly
 - Thrombosis of splenic vein
 - Carcinomatosis of the bone marrow
 - Lymphogranulomatosis, etc.
 - (b) *Infections* (typhoid fever, etc.)
 - (c) *Intoxications* (Benzol, Benzine, Arsphenamine).
 - (d) *Anaphylaxia*
 - (e) *Avitaminosis*

In this paper the diseases classified as symptomatic thrombopenic purpura (group II) will be excluded as it is Essential Thrombopenic Purpura (Essential Thrombocytopenia, Purpura Hemorrhagia, Werlhof's disease) alone that we wish to discuss. The important formed element of the blood in this disease is the thrombocyte or blood platelet which according to Wright³ is formed in the bone marrow from the megakaryocytes. This cell constricts or pinches off a portion of its granular protoplasm, which it throws into the circulation where it is known as the thrombocyte or the blood platelet.

Werlhof in 1781 was the first to separate purpura hemorrhagica from the other hemorrhagic diseases, though Lusitanus in 1557 reported a case of purpura occurring independently of the epidemic fevers, bleeding from the skin and mucous membrane having been recognized as occurring in pestilential epidemic for many years previous to this time. Among those who have written on this subject appear the names of LaRevere, Behrens, Horning, Willan, Schonlein and Henoch. Schonlein described its association with arthritis and Henoch its occurrence with abdominal pain and intestinal hemorrhage. The disease is one of early years, the majority of cases occurring in childhood. However cases have been reported to occur after the fortieth year of life. The incidence among women and men is in the ratio of two to one. Contrary, however, to this generally accepted ratio, McLean, Kreidel & Caffey⁴ in a series of twenty-one children under twelve years of age found seven females and fourteen males, the exact reverse of the above given ratio. They attribute this reversal to the absence of menstruation in the females of the younger group.

SYMPTOMS

The principal items in the symptomatology are spontaneous hemorrhage into the skin and mucous membranes, fall in total count of blood platelets, prolonged bleeding time, normal clotting time, nonretractile clot, and increased permeability of the capillary walls. The history is of spontaneous bleeding; nose bleeding, hemorrhages from the mucous membrane, excessive menstruation, ecchymotic hemorrhages and petechiae in the skin. The purpura may be of pin head size or larger and usually appears first on the lower part of the extremities. The hemorrhagic spots do not fade on pressure and undergo the color changes characteristic of extravasated blood. They appear in successive crops so that the color changes of all stages may be present at one time. The patient is bruised easily, especially over underlying bony structures as the tibia and iliac crest. Hemorrhages from the mucous membrane may be very large and may even lead to exsanguination. Bleeding from the nose and hematuria commonly occur. The stools may show frank or only occult blood. The vomitus often contains blood which usually is blood swallowed from the mouth or throat. Following hemorrhage

there is a drop in the hemoglobin and in the red blood cell count with a mild leukocytosis or normal white cell count. In the chronic type of purpura hemorrhagica attacks of bleeding may occur over a number of years with intervening symptom-free periods of varying length of time. The attacks also vary in length from a few days to months. Preceding the appearance of purpura of hemorrhage there may have been no symptoms whatsoever, or at most the history of some infection and the patient has usually been looked upon as in good health.

The cardinal points of this disease are closely interlaced one with the other and each has been carefully investigated. In order to bring out clearly the facts developed by this investigation, each cardinal feature will be separately considered.

THE PLATELET

During the attack the platelet count is found to be low, usually below 100,000. Denys⁵ is credited with having first called attention to the fall in platelets in 1887. Hayem⁶ in 1895 confirmed these observations. This feature of the disease was more thoroughly investigated by W. W. Duke⁷ who reported the results of his work in 1912. He was the first to observe the prolonged bleeding time and the close relationship between the platelets and the nonretractility of the clot. By observation of all patients with a tendency to bleed, over a period of three years, he separated a group whose bleeding was invariably accompanied by a marked fall in the number of blood platelets. He considered that the bleeding was due wholly or in part to this reduction in platelets, for the bleeding appeared when the platelet count fell to extremely low levels, persisted as long as the count remained low and disappeared when the count rose. While the association of a reduced number of platelets with the appearance of purpura and frank hemorrhage has been many times confirmed, still cases have been frequently reported in which hemorrhage has occurred with little or no reduction in the platelet count. Jones and Tocantins⁸ report several cases in which the other cardinal symptoms of the disease were present, including hemorrhage, but the platelet count was either normal or only slightly reduced. They are of the opinion that the essential feature of purpura hemorrhagica is not the reduction in number of platelets but rather the increased perme-

ability of the capillary walls. They however agree that the platelet plays an important part in this lowered capillary resistance.

A familial type of purpura hemorrhagica has been described by Glanzman,⁹ Rotham and Nixon,¹⁰ Minot¹¹ and others which they name Thrombasthenic Purpura. In this type the bleeding time is prolonged, the clot nonretractile and capillary resistance lowered, but the platelet count is normal. These cases however do not conform to Pratt's classification of Essential Thrombopenic Purpura in which, as the name indicates, the thrombocyte count is reduced and therefore the asthenic types are not germane to the subject being discussed. They are referred to only because they show that there is grave doubt that hemorrhage in this disease is due alone to the reduction in number of platelets.

The platelets are formed from the megakaryocytes or giant cells of the bone marrow. Their reduction below the normal number may be due to failure of these mother cells to produce platelets in sufficient number. The depressing influence of certain infections and toxins on the productivity of the bone marrow is well known, e.g., in aplastic anemia, where there is a general aplasia of all the hemoblastic centers, or again in neutropenia, where infections or toxins seem to affect the myeloblastic centers primarily. Aplasia of the bone marrow, involving the megakaryocytic center with consequent reduction of platelets, is seen in severe types of typhoid fever, measles, small pox, etc. In such cases the reduction of platelets in the general circulation is due to depressive effects exerted on the bone marrow, while the circulatory platelet is not involved. This depression of the bone marrow may result also in changes in the quality of the blood platelets.

Frank¹² in 1915 proposed the theory that the spleen exerts a toxic or inhibitory action on the megakaryocytes, which influence he thought was responsible for the reduction in the number of platelets. Minot¹³ found no reduction in the number of megakaryocytes in the bone marrow, but Brill and Rosenthal¹⁴ observed changes in the individual characteristics of the platelets and Koster¹⁵ called attention to disfunction of the bone marrow in this disease. The cells may be produced in normal quantity but due to some extramedullary factor may be destroyed in the general circulation. The removal of cellular debris from the circulation is performed by the reticulo-endothelial

system, a part of the function of which is to destroy and metabolize the weakened, damaged and senile blood platelets.¹⁶ The cells of the reticulo-endothelial system are found in the blood sinuses of the spleen, in the lymph nodes, the capillaries of the liver and bone marrow, in the connective tissue as wandering cells, and also in contact with the capillaries as Rouget's cells. The endothelial cells possess the peculiarity of being able to take up certain stains without disturbance of function.

Kaznelson¹⁷ believes that in thrombocytopenia the marked reduction of platelets is occasioned by an increased phagocytosis of platelets by endothelial cells, the disease being essentially due to a disturbance of the function of the reticulo-endothelial system. Koster¹⁸ in 1927 also observed this increased phagocytosis. The general opinion at the time favored the theory of Kaznelson and this theory suggested the thought of splenectomy, the favorable result of which has been a factor in confirming this belief. Further strength has been added to the view by vital staining of the reticulo-endothelial cells. Tyson¹⁸ states that when trypan blue is injected and is taken up by the cells of the reticulo-endothelial system, there follows an immediate rise in platelet count.

Cole¹⁹ in 1907 first demonstrated that the platelets could be destroyed in an animal by the injection of an antiplatelet serum from another animal. Lee and Robertson by the injection of an antiplatelet serum were able to produce a drop in the platelet count of guinea pigs from 300,000 to 10,000 in twenty-four hours. The antiplatelet serum in these experiments also brought about other changes in the blood similar to those found in purpura hemorrhagica, namely the bleeding time was increased from two to fifty minutes and the clot failed to retract. We do not know whether the platelets are destroyed by increased phagocytosis or whether an abnormal quality of the platelets is responsible for their removal from the circulation. By some destruction of platelets is thought to be caused by some toxin or antiplatelet serum. One or all of these forces may be at work.

COAGULATION AND CLOT

The clotting of thrombopenic blood in a test tube is either normal in time or only slightly prolonged, but the clot is lacking in firmness

and does not retract in the normal manner. This failure of the clot to retract associated with normal coagulation time was first noted by Hayem⁶ in 1896. E. Glanzman²⁰ found that the platelets are the only formed element of the blood which undergoes decomposition in the normal clot, and he is of the opinion that they thereby accelerate the process of coagulation. Reubens and Cleman²¹ quote the observation of Burke and Tait on this phenomenon under dark field illumination, "The platelets burst and the protoplasm is projected rapidly in all directions. Along these particles threads of fibrin are laid down. When the platelets were experimentally removed, the blood remains fluid indefinitely unless tissue extract or platelets were added." In cut or injured blood vessel the opening is closed by contraction and by the formation of a thrombus at the site of injury. Any interference with the formation of the thrombus or contraction of the vessel would result in prolonged bleeding. For a clearer understanding of the processes of thrombus formation, we quote the following from McCallum's Text Book on Pathology,²² "A thrombus begins by the deposition on the wall of the blood channel of a minute, pearly, translucent mass of platelets which grows by the adhesions of other platelets as they come by. These produce curious upstanding laminae or walls running transversely to the blood stream and anastomosing freely with one another; the platelets are so welded together that their outlines can no longer be seen, and in section these laminae appear as faintly pink-staining, finely granular bands in the substance of the thrombus. However, it must not be supposed that they rise up alone and unsupported in the current. Instead of that, they quickly catch the passing leucocytes and hold them all along their surfaces like flies on a sheet of sticky fly-paper; and at the same time they seem to liberate thromboplastic substance so that filaments of fibrin spread out from them on all sides and meeting with filaments from the next lamella, hang in festoons between them. In this way the branching and anastomosing lamellae are guyed and braced together by fibrin, which needless to say, entangles quantities of red corpuscles, so that finally the whole is a solid mass of peculiar constructed clot."

These quotations reveal the important and fundamental part played by the blood platelets in normal clotting and in thrombus formation, and through these processes on the length of bleeding time.

Brill and Rosenthal¹⁴ believe that qualitative changes in the platelet are responsible for the failure of clot retraction. They found the platelets in thrombocytopenia to be larger than normal and irregular in shape. They think this abnormality due to faulty fragmentation of the pseudopods of the megakaryocytes and suggest some damaging influence on the formation of platelets, which alters their properties of agglutination, clot, and thrombus formation. This agency they believe may reside in the reticulo-endothelial system, particularly that of the spleen. Their suggestion of platelet qualitative change is based in part on their findings that in pernicious anemia, leukemia, and a few cases of secondary anemia, the bleeding time was not prolonged though the platelet count be below 10,000, and the platelets apparently of normal quality.

LOWERED CAPILLARY RESISTANCE

An essential factor in the bleeding in this disease is the lowered capillary resistance—the hyperpermeability of the capillary walls. Not only does serum escape through the cellular interstices but the cellular elements of the blood as well. Lowered capillary resistance is demonstrated by the application of the capillary resistance test of Hess.²³ If a tourniquet is applied lightly to the arm, sufficiently tight to block the venous flow, but not the arterial pulse, and allowed to remain in place for five minutes, small capillary hemorrhages appear on the limb below the point of constriction. The Rumpel-Leads test modifies this technique by using the sphygmomanometer and raising the mercury to a point below the systolic pressure. This gives a more accurate gauge of the amount of pressure applied.

Rouget in 1873 described a large contractile cell in the capillary wall which irregularly encircles the capillary and which bears his name. Aschoff classed these cells as a part of the reticulo-endothelial system. Whipple²⁴ says that it is conceivable that these Rouget cells, stimulated by the same agent that is active in other parts of the reticulo-endothelial system may disturb the capillary walls and facilitate the escape of blood. Another factor in this hyperpermeability may be the softening of the intercellular cement substance of the endothelial cells in the walls as observed by Aschoff.¹⁰

The action of defibrinated blood or blood serum in causing vasoconstriction has been known for some years. Ludwig²⁵ in 1868

and Mosso²⁶ in 1874 first observed this phenomenon which was confirmed later by other observers, especially by O'Connor²⁷ in 1911-1912. This author states that a substance is thrown into the plasma or formed in it during the process of clotting which is responsible for the action. Stewart and Zucher²⁸ write as follows: "An extract of blood platelets of citrated blood, the plasma of which is totally inactive, exerts a strong constriction on the arterial ring". Janeway, Richardson & Parks²⁹ demonstrated that the platelets yield a substance which has a powerful vasoconstrictor action. The red blood cells and leukocytes yield none. This vasoconstriction is probably due to changes which occur after the plasma leaves the blood vessels, for the circulating plasma does not cause vasoconstriction. This vasoconstricting substance, though present in coagulated blood, is not dependent upon the actual formation of the clot, nor is it related to any factors concerned with coagulation, with the possible exception of thromboplastin. Hirose³⁰ added further details to our knowledge of the process by showing that the vasoconstriction is roughly proportionate to the number of platelets in the circulating blood and that in blood with platelet counts far below normal there is practically no vasoconstricting action. Brill and Rosenthal after referring to the work of O'Connor and Janeway seem to think that any disturbance in the production or function of the platelets, may bring about a bleeding tendency from the effect of this disturbance on the capillaries. That there is a relation between the blood platelets and the capillary tone seems to be true. It is also true that failure of capillary tone may increase capillary leakage. Janeway's experiments show that the substance responsible for this vasoconstricting action of blood serum is derived from the blood platelets. If so, any change in the quality of the platelet could affect the supply of the vasoconstricting substance, and consequently influence vasomotor tone. McLean⁴ states that the severity of the capillary bleeding is not in proportion to the number of platelets, severe bleeding occurring in the presence of platelet counts varying from 10,000 to 104,000. The lowered capillary resistance seems to be due to the activity of some agent responsible for the changes in quality and number of the platelets and also for the irritation of Rouget's cells and the softening of the intercellular cement substance of the capillary walls.

ETIOLOGY

The etiology of essential Purpura Hemorrhagica is unknown. In the symptomatic type, infection, drug intoxication, anaphylaxis, food deficiencies and primary disease play the activating role, but no definite cause of the essential type has as yet been discovered. The large amount of effort expended in investigating the disease has added greatly to our knowledge of the symptoms but has thrown no light on its etiology. The primary causative agent may be an infection or perhaps a toxin coming from the spleen, lymph tissues or bone marrow.

PATHOLOGY

The pathology of the blood and blood making organs has been treated in the foregoing paragraphs and there is but little more to say about it. Enlargement of the spleen is not a constant symptom and the organ is palpable only in a small number of cases. Actual enlargement occurs in only one third of the cases. Most of the specimens examined show some evidence of splenitis and tuberculosis of the spleen has been found in several cases but otherwise the pathological changes found in the spleen are not of diagnostic value.

DIAGNOSIS

The presence of hemorrhage, low platelet count, prolonged bleeding time, nonretractile clot and lowered capillary resistance as shown by the Rumpel-Lead test clearly establish the diagnosis. Differentiation from the secondary purpura due to sepsis, drugs and avitaminosis is at times difficult. Hemophilia, Henoch's purpura, leukemia, pernicious anemia, aplastic anemia, malignant metastasis to the bone marrow may at times cause confusion. In chronic recurring thrombocytopenia presenting the classical symptoms, there are few difficulties, but in the atypical cases great care must be taken, as upon the diagnosis will depend in a measure the success or failure of the treatment.

Henoch's purpura will be accompanied by acute abdominal pain and possibly hemorrhage from the bowels. Hemophilia occurs only in males with the characteristic hereditary trait of transmission through the female, thrombocytopenia occurring mostly in females.

Hemophilia is an exceedingly rare disease and usually trauma precedes hemorrhage. All the blood phenomena are normal except prolonged clotting time. In avitaminosis there is the history of dietary deficiency as in scurvy, in which disease there is the swollen spongy condition of the gums, pain in the limbs and little tendency to prolonged bleeding. The blood picture is practically normal. Leukemia associated with hemorrhage will present difficulties in the aleukemic stage, but in the cases of long standing where the bleeding occurs late, the typical blood smears show clearly the picture.

In pernicious anemia, hemorrhages also occur late in the course of the disease after the bone marrow has become exhausted and the aplastic stage is approached. Aplastic anemia offers the most difficulty, as the bleeding occurs early and is associated with low counts in all the formed element of the blood. Fortunately in purpura hemorrhagica there is a leukocytosis or a normal white count and the regenerative abilities of the marrow are intact as far as the red and white cells are concerned. This is shown by the presence of leukocytosis and an increased number of reticulocytes. The presence of increased white blood cells and reticulated red cells is of the utmost importance, for they show a bone marrow that is capable of supplying the necessary formed elements of the blood if the destructive agent is removed and is of great importance in differentiation from anemia aplastica.

CHART

Differential blood diagnosis⁸¹

Both show thrombocytopenia.

Aplastic Anemia

Low R.B.C., progressive

Few reticulated R.B.C.

Low W.B.C. (Leukopenia)

Low Polymorphonuclears

Lymphocytosis

Platelets reduced, often late

Platelets not affected by splenectomy

Bilirubinaemia

Purpura Hemorrhagica

R.B.C. variable, due to periods of bleeding

Many reticulated R.B.C., occasional normoblast

W.B.C. normal or increased

Polymorphonuclears above 50%

No lymphocytosis

Platelets always reduced

Platelets always increased after splenectomy

No bilirubinaemia

Metastasis of malignant growth to the bone marrow by proliferation crowd out the haemoblastic centers and thereby produce a reduction in the number of circulating cells of all of the formed elements of the blood. Careful search must be made for possible primary growth. The aplasia of the bone marrow due to such metastasis would present the blood picture of an aplastic anemia rather than a thrombocytopenia. Careful search should also be made for all foci of infection and for possible bacterial endocarditis.

Grove³² recites a new test for the regenerative powers of the bone marrow, "If a few minims of adrenalin are given hypodermically, the platelet count will rise to normal in pernicious anemia, while in thrombocytopenia there will be a slight rise and in aplastic anemia there will be none at all.

TREATMENT

The treatment of Purpura Hemorrhagica is as yet in the experimental stage. Though much work has been done on the disease during the past twenty-five or thirty years, so little light has been thrown on the etiology that the establishment of a definite line of treatment has been impossible. Such attacks as have been made upon the problem have recommended themselves because the course and symptomatology of the disease seem to be favorably modified by these measures and many cases are apparently cured. In other cases atypical and unexpected results following these measures show very clearly that the present methods of treatment do not reach the root of the disease and are therefore directed against the symptoms rather than against the cause. A review of the literature shows that the whole endeavor is still of a prospective nature and that the final work, an adequate treatment, cannot be perfected until a proper classification based on known living pathology and proved etiology, is completed. In the milder cases there is frequently spontaneous recovery and Giffin³³ recommends that these incipient cases be treated by rest and medical measures (as iron in large doses and proper diet) together with careful elimination of all foci of infection and, if needed, transfusion and possibly irradiation of the spleen. Other writers are inclined to think that there is loss of valuable time in such expectant treatment and in the face of a disease that may become acute or develop an emergency at any moment, to delay is to court dis-

aster. McLean⁴ states that there are cases, both mild and severe, acute and chronic, in which recovery occurs without either transfusion or splenectomy.

Rankin³⁴ says that unquestionably splenectomy is the most satisfactory treatment of Essential Purpura Hemorrhagica and cites forty cases treated by this method at The Mayo Clinic, with no deaths, to back his statement. After two years these patients were well and in good health. He believes that the earlier the operation the better are the results. Whipple²³ reports a series of eighty-one collected cases of this disease, treated by splenectomy, seventy-three of which were of the chronic type and eight of the acute. In the seventy-three chronic cases there were six deaths following removal of the spleen and in the acute cases seven deaths out of eight. He believes that splenectomy is the method of choice in the treatment of the chronic type. Pemberton³⁵ thinks splenectomy is as safe as any other major abdominal operation and that few operative measures offer such spectacular results. Payne³¹ says that splenectomy should be done as early as possible in the course of the disease to forestall the aplastic changes in the bone marrow which result from exhaustion of these centers through continued hemorrhage and extramedullary blood destruction. While splenectomy offers more than anything else in the treatment of these cases, a proper selection is necessary for the best results. In the acute cases the spleen should be removed if possible during remission. In the mild incipient cases, splenectomy should be prompt to avoid the destructive action of the toxins on the blood making organs and further destruction of the blood elements. Great care should be used in identifying and eliminating the thrombasthenic type. Askey and Toland³⁶ have shown that this type is not benefited by the removal of the spleen. In the chronic type the general opinion is that splenectomy offers most and gives the highest percentage of cures. Careful search should be made during the operation for an accessory spleen, which may be responsible for a return of the symptoms. Morrison, Lederer and Fradkin³⁷ describe a case in which they did not remove a small accessory spleen and the symptoms returned within a year. The result of splenectomy will depend in great measure upon the regenerative power of the bone marrow. It is upon this capacity for regeneration that Payne³¹ has formulated his index of opera-

bility. This index is briefly as follows: The presence of leukocytosis or a normal white cell count, plus increased or normal number of reticulated red cells indicates an active bone marrow, one capable of restoring to the blood stream the necessary cellular elements if the destructive agent is removed. The presence of leukopenia plus reduction in or absence of reticulated red cells shows an aplastic bone marrow which is incapable of supplying these elements under any condition. In the presence of an active bone marrow good results may be expected following splenectomy, but in the presence of an aplastic marrow, splenectomy is of no benefit, for the bone marrow is exhausted. It seems proper to recall the differential diagnosis between thrombocytopenia aplastic anemia, which is based largely upon this very difference in activity of the haemablastic centers. It is possible, nay probable, that in some of the reported cases in which death has followed splenectomy, there had been a failure properly to note this index. To recapitulate: given an active bone marrow in this disease the spleen should be removed as early as possible; in the presence of an exhausted or aplastic marrow, splenectomy is contraindicated.

Transfusion may check the course of an acute fulminating case and hasten a remission. It is of special value when the risks of splenectomy seem too great after extensive loss of blood. By checking the hemorrhage and replacing the lost blood elements even for a short period of time the patient is in far better condition to withstand the shock of surgical removal of the spleen than without such assistance. Though recovery follows transfusion in some cases the percentage of apparent cures is by no means as high as splenectomy in all types. McLean⁴ in his series reports eight cases treated by transfusion with recovery in four. We feel that the proper place for transfusion is in the preoperative treatment. It is our custom to transfuse every other day until three or four transfusions have been given. In this way the patient's blood is built up through stimulation of the regenerative processes in the bone marrow as well as by replacement of the lost blood. Should the expected improvement in the patient's condition take place, the transfusions are followed by immediate splenectomy. Taylor³⁸ reports the use of antivenin, both of the crotalic and the bothrops atrox varieties

in a small number of cases with good results; but as yet the cases reported are too few to form a sound opinion of its value.

DISCUSSION

The foregoing facts gleaned from a careful review of the literature of the past fifteen years show a steadily increasing trend of conviction along two important lines.

First, that the benefits resulting from the removal of the spleen are available in a larger percentage of cases than was formerly believed. Successful operations have been performed on the acute fulminating type, whereas formerly the operation was considered safe only in the chronic type. This is due to closer observation and more rigid selection of cases. With the elimination of the atypical types such as thrombasthenic purpura and of the symptomatic cases in which the thrombocytopenia is due to known causes, and with a closer observance of the Payne index covering total white count and reticulated red cell count, we may hopefully expect a more favorable recovery in those cases which are subjected to splenectomy.

Secondly, that the clinical manifestations of the disease are not due to a mere diminished number of circulating platelets, but to some other factor as yet undetermined. Upon Kaznelson's statement of the increased phagocytosis of platelets by the endothelial cells and the cessation of such increased activity upon the removal of the spleen it was assumed that the pathological process was of a very simple nature, to wit, that phagocytosis on the part of the endothelial cells was responsible for the reduced number of platelets and that the reduction of platelets below the normal level was in turn responsible for the abnormalities of clot formation, bleeding time and capillary resistance, and through these abnormalities for the purpura and hemorrhage. The situation is not so simple.

It has been clearly shown that reduction of platelet count is not necessarily responsible for these abnormal blood conditions, nor for the hemorrhage. Observations are here quoted showing reduced number of platelets without hemorrhagic manifestations and conversely, spontaneous hemorrhage into the skin and mucous membranes in the presence of a normal platelet count; also nonretractile clot, prolonged bleeding time and lowered capillary resistance associated with a normal platelet level. It is known that normal throm-

bus formation is one of the means of stopping or preventing leakage of blood through the vessel walls and that normal thrombus formation and normal clotting are dependent in a great measure on the blood platelets. The presence of normal clotting time and a retractile clot in pernicious anemia with an extremely low platelet count would indicate that it is not alone the reduction in the number of platelets that is responsible for these abnormalities of the clot. The same is true also in thrombaesthenic purpura, in which abnormalities of clot formation exist with a normal number of thrombocytes. The fault is therefore not in the number of platelets but in their quality. If the quality of the platelet is good, normal clotting will take place even though the number of platelets be greatly reduced. This is an important fact. Frank, Lee and others have suggested that some hypothetical toxin is responsible for these changes. The activity of this toxin cannot be confined simply to the destruction of platelets. It may act as Whipple suggests on the capillary walls, and on the qualitative formation of platelets as observed by Brill and Rosenthal. It is the opinion of Frank that the increased phagocytosis of the reticulo-endothelial cells is due to stimulation or irritation by a toxin. In short the theory of toxin activity may explain all the features of the disease. The cessation of bleeding and oozing upon clamping or tying off the pedicle of the spleen is so striking and immediate that it has attracted the attention of many writers and suggests the presence in the blood stream of some substance peculiarly responsible for the hyper-permeability of the capillary walls. It does not seem possible for the lowered capillary resistance to be the result of reduction of platelets alone, for the cessation of the bleeding on tying the splenic pedicle could then be due only to a rise in platelet count to the point of correcting the lowered capillary resistance. It is well known that the platelet count does rise rapidly after removal of the spleen and also following trauma at points remote from the spleen, but not at so spectacular a rate. Following splenectomy for purpura hemorrhagica the bleeding is staunched almost immediately, in some cases before the abdominal incision is closed or the patient leaves the table, as we ourselves have seen, although the platelet count reaches normal at the earliest in two or three days. This striking occurrence suggests the presence in the blood stream of a toxin which tends to lower capillary

resistance yet so transient in its effect that a continuous supply is necessary for sustained action. It is evident that the spleen is the source of this supply, since that organ is the only one cut off from the general circulation. That the spleen is the sole source of the toxin does not seem to be the case, for recurrences are reported following splenectomy. Askey and Toland³⁶ state that many cases show clinical improvement with relief of hemorrhage after surgical removal of the spleen, but fail to show improvement in the condition of the blood; the platelets remain low, the bleeding time is prolonged, the tourniquet test is positive and the clot nonretractile. It is probably true that the entire reticulo-endothelial system is diseased and that the removal of the spleen is only a quantitative reduction in the extent of the disease.

Until through research a proper classification of the various types of purpura hemorrhagica on a basis of proved etiology and pathology has been made, no assured course of treatment can be outlined. Thus far, splenectomy offers most in the treatment of this distressing and terrible disease.

REFERENCES

- ¹ EPPINGER, H.: "Enzyklopadie der Klinischen Medizin," 1920.
- ² OSLER, AND MCCREA: System of Medicine.
- ³ WRIGHT, J. H.: *Boston M.& S.J.*, 154:643, 1906.
- ⁴ MCLEAN, KREIDEL, AND CAFFEY: *J.A.M.A.*, 98:387-393, 1932.
- ⁵ DENYS, J.: *La Cellule*, 3:445, 1887.
- ⁶ HAYEM, G.: *Presse Med.*, 3:2333, 1895.
- ⁷ DUKE, W. W.: *Arch.Int.Med.*, 10:445, 1912.
- ⁸ JONES, H. W., AND TOCANTINS, L. M.: *M.Clin.North America*, 16:181-197, 1932.
- ⁹ GLANZMAN, E.: *Jahrb.f.Kinderh.*, 88:1, 113, 1915.
- ¹⁰ ROTHMAN, P. E., AND NIXON, N. K.: *J.A.M.A.*, 93:15-17, 1929.
- ¹¹ MINOT, G. R.: *Am.J.M.Sc.*, 175:301, 1928.
- ¹² FRANK, E.: *Berl.klin.Wchnschr.*, 52:454, 490, 1915.
- ¹³ MINOT, G. H.: *Arch.Int.Med.*, 19:1071, 1917.
- ¹⁴ BRILL, AND ROSENTHAL: *Arch.Int.Med.*, 32:939, 1923.
- ¹⁵ KOSTER, HARRY: *M.J.& Rec.*, 125:23, 97, 167, 1927.
- ¹⁶ ASCHOFF: "Lectures on Pathology," New York, P. B. Hoeber, 1924.
- ¹⁷ KAZNELSON, P.: *Wein.klin.Wchnschr.*, 29:1451, 1916.
- ¹⁸ TYSON, RALPH M.: *J.A.M.A.*, 98:393, 1932.
- ¹⁹ COLE, R. I.: *Bull.Johns Hopkins Hop.*, 18:261, 1907.
- ²⁰ GLANZMAN, E.: *Jahrb.f.Kinderh. und Physiche Erziehung*, 83:271, 379, 1916.
- ²¹ REUBENS, M. S., AND CLEMAN, L.: *Arch.Pediat.*, 45:84, 1928.
- ²² MCCALLUM: "A Text Book of Pathology," p. 9, W. B. Saunders.
- ²³ HESS, A. F.: *Arch.Int.Med.*, 17:203, 1916.

- ²⁴ WHIPPLE, A. O.: *Surg.Gynce.& Obst.*, 42:329, 1926.
- ²⁵ LUDWIG, C., AND SCHMIDT, A.: *Arb.a.d.physiol.*, 1808.
- ²⁶ MOSSO, A.: *Arb.a.d.physiol.*, 1874.
- ²⁷ O'CONNOR, J. M.: *München.med.Wohnschr.*, 2:1439, 1911; *Arch.of Exper.Path.& Path.*, 1912.
- ²⁸ STEWART, G. N., AND ZUCKER, T. F.: *J.Exper.Med.*, 17:152, 174, 1913.
- ²⁹ JANEWAY, RICHARDSON, AND PARKS: *Arch.Int.Med.*, 21:505, 1918.
- ³⁰ HIROSE, K.: *Arch.Int.Med.*, 21:505, 1918.
- ³¹ PAYNE, R. L.: *Internat.S.Digest*, 6:74, 1928.
- ³² GROVE, LON, AND MONFERT, J. M.: *Southern Surgical Transactions*, 44:104, 1931.
- ³³ GIFFIN, HERBERT: *Collected Papers of Mayo Clinic*, 1932.
- ³⁴ RANKIN, FRED W.: *Ann.Surg.*, 93:752, 1931.
- ³⁵ PEMBERTON, JOHN DE J.: *Ann.Surg.*, 94:755, 1931.
- ³⁶ ASKEY, J. M., AND TOLAND, C. G.: *Arch.Surg.*, 26:103, 1933.
- ³⁷ MORRISON, M. D., LEDERER, M., AND FRADKIN, W. Z.: *Am.J.M.Sc.*, 176:672, 1928.
- ³⁸ TAYLOR, K. P. A.: *Am.J.Surg.*, 21:285, 1933.

ESTIMATING THE EXTENT OF DISABILITY

By EARL D. McBRIDE, M.D., F.A.C.S.

Oklahoma City, Oklahoma

WHEN we testify in industrial court how shall we answer when this question is asked? "Now, doctor, what in your opinion is the extent of permanent disability in this case?"

Most of us will admit that we would like very much to avoid such a question; probably because we feel more or less unprepared to answer in as capable a manner as questions of a professional nature should be answered. Whatever the opinion expressed, reliability must be implied. The responsibility of answering the question is professionally as great as participation in consultation at the bedside. In fact, the influence of medical testimony reaches far beyond the scope of the general practice of medicine. Medical conclusions, often at best, controvertible, hypothetical and equivocal, must be publicly expressed to non-medical inquisitors, and judged through legal prerogatives. The difficulty for the doctor lies in the exigency of a common ground of reasoning in determining the extent of permanent disability.

The court wants definite information with "yes" and "no" answers to questions formulated in the minds of examining attorneys, each trying to draw out evidence that will convince the court in favor of his client. If the physician's testimony is to be any more accurate than the claimant's own statement of his complaints, there should be a sound basis of reasoning and a common ground acknowledged by physicians to be proper fundamentals upon which to base their opinions. It is sometimes astounding how widely apart testifying physicians will be in their percentages of disability in a given case. Temporary disability is often misinterpreted as permanent disability through a lack of understanding of what constitutes the healing period. Take for example this case:

R. A. A.:—Age forty-one. Received a compound, comminuted fracture of his left tibia and fibula on December 4, 1926 in an oil rig accident. He was examined in this clinic on October 17, 1928.

The fracture healed by angulation and overlapping consisting of an outward and anterior bowing at the junction of the middle and lower thirds, of about 10° . In standing the heel cord was contracted so that the heel could not touch the floor without placing the foot forward. The calf of the leg and the ankle were still somewhat swollen and the scar although well healed was still red and somewhat tender. There was no drainage. The history showed that he had active surgical treatment in the hospital for approximately five months and at the end of three months more, returned to the hospital where some sequestration was removed from the leg. He was dismissed from all medical treatment at the end of fourteen months. He returned to work in the oil field on September 10, 1928, which was one year and ten months after the injury. The leg was still somewhat swollen and continued to give him considerable discomfort.

When he was examined in this clinic on October 17, 1928, he had been at work approximately one month and his case came up for final award. The medical testimony consisted of opinions of three physicians; one gave him 100% loss of use of the leg, another an estimate of 75% loss of use of the leg, and he was awarded a loss of 82%.

The opinions were based chiefly on the effect of the deformity and the fact that occasionally there was a lighting up of tenderness and inflammation in the scar tissue in the region of the injury. He was seen again in this clinic on January 25, 1933, which was three years and two months after his settlement. He claimed to have had a change for the worse and had filed a motion for reopening of his case. It was found that he had an abscess forming on the outer side of his ankle and that during the past three years he had had several exacerbations of inflammation and on one or two occasions small bits of bone had worked out of the wound.

On June 1, 1933, in another clinic, his leg was amputated about 5 inches below the knee. IN THIS CASE, it was quite evident that settlement was made before the final healing period had been reached; an error commonly made.

Another instance is as follows: C. R. W.—Age twenty-seven. Received a comminuted fracture of the left humerus on May 28, 1931, in a truck accident. He was examined in this clinic on November 13, 1931, five and one-half months following injury. The

history showed that he received active surgical treatment until October 15, and was discharged from treatment on November 10, 1931. On examination he was still complaining of pain and weakness in the arm. It was found that the arm had in general a normal appearance. The muscles were of poor tone. There was no swelling. There was normal motion at the shoulder, elbow and wrist joints, with no paralysis. He could fully close and open the hand and seemed to have practically as good grip in one hand as in the other. The bone of the left upper arm could be felt to be somewhat irregular in outline along the middle third, but union was firm and there was no angulation. He also had an injury to his leg and side, which had healed with no residual disability or loss of function.

On December 10, 1931, testimony in his trial at the Industrial Commission was given in which one physician stated that he had 100% loss of use of the arm, another 27.5% loss of use of the arm, and still another said that his maximum healing period would not end for about two or three months more and that he should then not have any permanent disability. He was awarded 75% loss of use of the arm.

It was later found that he returned to hard manual labor and apparently suffered no permanent disability whatever.

With such wide differences in medical opinion, the court is left in a dilemma and the judgment may be unreasonable. To avoid disapprobation and to promote confidence, medical evidence should be more consistent and more conventional. Legal requirements are satisfied, as well as the medical witness qualified, by one who has a proper degree and license to practice medicine. Why not provide instruction during the period of medical training, which will acquaint every practicing physician with what is expected of him in these modern days of medical practice. In medical school and in practice, the physician has not learned to go beyond the healed state. That is, there has not been much effort to teach what deformity means to the person after he has reached the final healing state. Such subjects as diagnosis and treatment are stressed only to the point of prevention of such deformity and disability, but the interest ceases in the patient after treatment no longer is necessary. The altered physiological state and the mechanical influence of the de-

formity and disability should at least have some expression in fundamental medical knowledge.

In the past, medical practice has been individualistic. Whatever might happen to the person through handicap was his own responsibility. Sociological development has brought about a new demand upon medical practice. Society has become interested in the person and wants to know about him, and his welfare. In case of injury, society is not so greatly interested in the treatment of the person. It becomes particularly interested, however, when, as a result of a physical handicap, a man is unable to take his normal position and rank in the rivalry of competition and the antagonism of existence to environment.

Society, through the industrial court, cannot arrive at conclusions about how much a man is disabled from following his duties as a laborer, without medical evidence. Testimony cannot be intelligently given by a physician unless he has some conception of how to measure disability. He must learn how to diagnose the altered physiological state and the limitation of function just as he has learned to diagnose disease. That is, when a person has been transformed into one with a physical handicap, there must be evolved some systematic and scientific method with which the extent of disability can be determined. Physiologists have done this very thoroughly in respect to normal development. Fischer, Steinhausen, Simonson and others have shown the physiological differences between an athlete or contortionist before and after development of such unusual accomplishments.* Through similar principles of logic conclusions may be deducted in respect to the altered physiological state resulting from pathologic causes. Text books on injuries cease comment on the pathological state after presenting the methods for preventing and re-instating the damaged anatomy to as near normal as possible. Statements such as "shortening will produce serious disability", "angulation should be prevented", and "ankylosis may produce a marked limp" are about as near as the final altered physiologic state is expressed.

The effect of the anatomical and physiological alterations must be interpreted in respect to their effect on functional ability, and

* Articles by O. Fischer, Wilhelm Steinhausen and E. Simonson in *Hanbush der Normalen und Pathologischen-physiologie* Vol. XVI.

what will be the limitations and possibilities of adaptation to environment. Will it be possible for the person to resume normal physical activity? If not, why not, and to what extent will he be limited? The industrial court is concerned chiefly with the effect of a physical handicap on the working capacity. That is, the ability of the man to perform ordinary manual labor. To what extent will the physical impairment limit the laborer from performing the work which he must perform to gain a livelihood? What is the working capacity since the handicap has occurred?

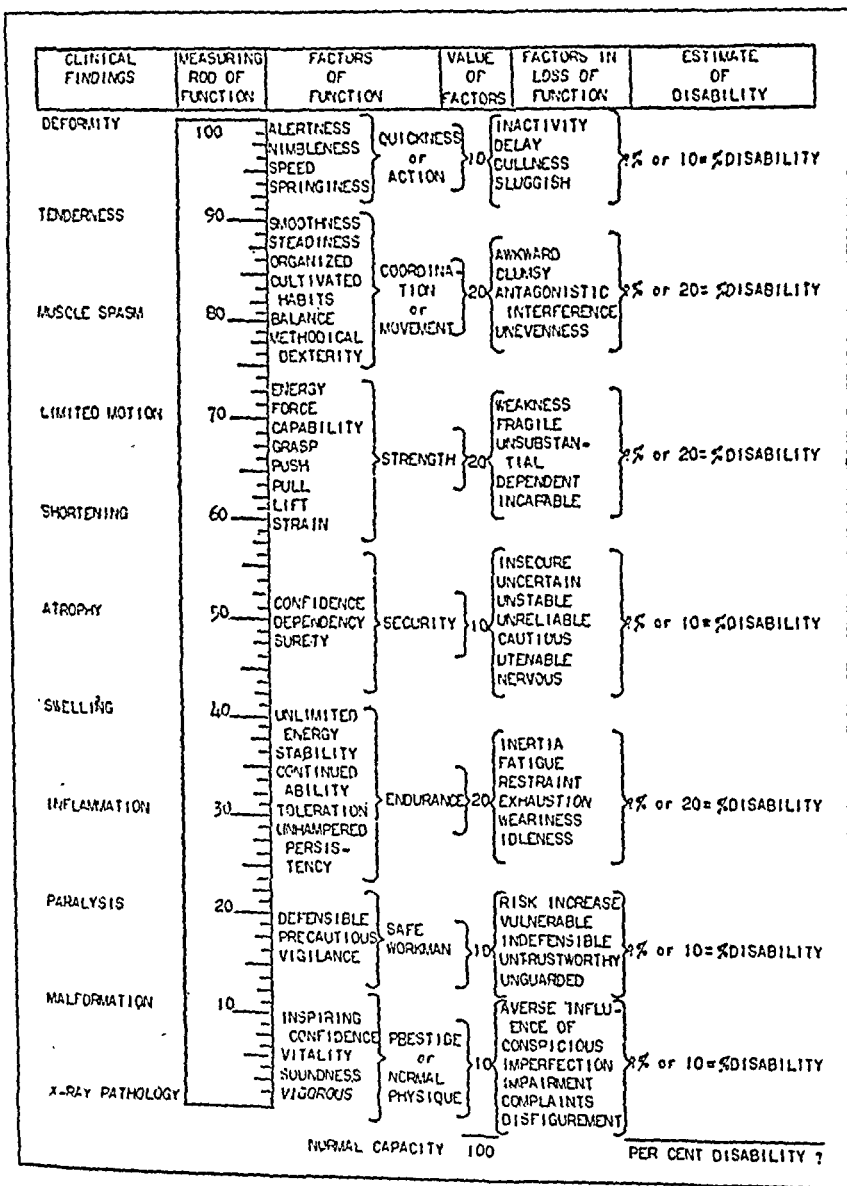
From embryo to full development the biological characteristics of man are animated by intrinsic qualities peculiar to the human organism. The capacity of the organism to meet the resistance of environment varies in each person, according to hereditary traits, habits, ambitions, constitution and many other qualities of development. Through disease, injury or other causes, the natural state peculiar to the person affected, is suddenly changed. As a result of anatomical alterations, new physiological adaptations are necessary. The habits and attainments of organic maturity must be reorganized.

When such wide differences of opinion exist, as were expressed in the case of C. R. W., it is evident that the personal experience and impressions of the physician have been allowed to dominate his reasoning, instead of being guided by the effects of clinical, physiological and anatomical limitations. One doctor may be greatly impressed by the possibility of the deformity producing so much weakness that it may prevent work; another may place a great deal of weight on the patient's statements of despair and still another may base his conclusion chiefly upon the inability of the patient to return to his former vocational calling.

The purpose of this discourse is to outline and suggest a fundamental basis of reasoning in determining permanent disability. If carefully considered, it will be seen that the extent of disability cannot be based on vocational loss because the physician may not have had experience in the particular vocation in question and he, therefore, cannot always be qualified to say whether or not a man can go back to his particular form of work. Furthermore, the person might accommodate himself to some other vocation and produce an even greater earning ability than before injury. The extent of disability, likewise, is not to be based on anatomical loss although most

compensation schedules express a specific award for anatomical loss such as amputation. However, in partial permanent disability this method cannot be relied upon as accurate. For instance, 50 per cent.

CHART I



Evaluation of extent of disability.

CHART No. II. EVALUATION OF EXTENT OF DISABILITY

in the hand or arm

Clinical Findings	Measuring Rod of Function	Factors of Function	Values of Factors	Factors in Loss of Function	Estimate of Disability
DEFORMITY	100	— Finger nimbleness, — striking, alertness, — grasping, speed, — reaching.	QUICKNESS OF ACTION	10	{ Inactivity, delay, dull- ness, slug- gishness } 7% of 10 is % disability
TENDERNESS	90	— Dexterity of fin- ger, thumb, palm — action.	COORDI- NATION OF MOVEMENT	20	{ Awkward, clumsy, an- tagonistic interference. Loss of skilled attainments } 7% of 20 is % disability
MUSCLE SPASM	80	— Synchronizing — movements with — other hand and — body movements. — Skilled — attainments			
LIMITED MOTION	70	—			
SHORTENING	60	— Power of grasping, — gripping, — pinching, — pushing, — turning, — striking	STRENGTH	20	{ Weakness of grasping, grip, pinch, push } 7% of 20 is % disability
ATROPHY	50	— Confidential — surety. Finger, — palm, action. Reli- — ability of touch — and special sense	SECURITY	10	{ Unreliable finger, thumb, palm action. Added cau- tiousness } 7% of 10 is % disability
SWELLING	40	—			
INFLAMMATION	30	— Accomplishments — of — technical — ability. — Stability of — grasp, grip, — pinch, push, — turning.	ENDUR- ANCE	20	{ Exhaustion, limited persistency } 7% of 20 is % disability
PARALYSIS	20	— Defensive ability — Normal sense of — caution in finger — and arm.	SAFETY AS A WORKMAN	10	{ Vulnerability of stiff fin- gers or arm. Unguarded attempt to use reliable parts } 7% of 10 is % disability
MALFORMATION	10	— Soundness of — appearance — in fingers — and arm.	PRESTIGE OF NORMAL PHYSIQUE	10	{ Adverse influ- ence of im- paired fingers or arm } 7% of 10 is % disability
ROENTGEN-RAY PATHOLOGY	—	—			

CHART No. III. EVALUATION OF EXTENT OF DISABILITY

in foot or leg

Clinical Findings	Measuring Rod of Function	Factors of Function	Value of Factors	Factors in Loss of Function	Estimate of Disability
DEFORMITY	100	— Springiness — of step or — gait. Alertness — in walking, — running, — jumping, — kicking.	10	{ Reduced activity of gait and movements }	{ 7% of 10 is % disability }
TENDERNESS	90	— Steadiness of — foot and toe — action. Syn- — chronizing — movements — with other — leg and body. — Skilled attain- — ments.			
MUSCLE SPASM	80	— Strength of — weight bearing — standing, — walking, running, — kicking or — jumping.	20	{ Awkward, clumsy, antagonistic interference. Loss of skilled attainments }	{ 7% of 20 is % disability }
LIMITED MOTION	70	— Confidential — surety of — foot, toe and — leg action.			
SHORTENING	60	— Toleration of — continuous — standing, walking, — running, — jumping, or — kicking.	20	{ Exhaustion, limited persistency }	{ 7% of 20 is % disability }
ATROPHY	50	— Defensive ability — of leg — and foot. Normal — sense of — caution in toe, — foot and leg.			
SWELLING	40	— Soundness of — appearance of — gait and — movements	10	{ Vulnerability of stiff foot, toe or leg. Unguarded attempt to use reliable parts }	{ 7% of 10 is % disability }
INFLAMMATION	30	—			
PARALYSIS	20	—	10	{ Averse influence of impaired gait or movements }	{ 7% of 10 is % disability }
MALFORMATION	10	—			
ROENTGEN-RAY PATHOLOGY					
Normal Capacity			100		

CHART NO. IV. EVALUATION OF EXTENT OF DISABILITY
in the eye

Clinical Findings	Measuring Rod of Function	Factors of Function	Value of Factors	Factors in Loss of Function	Estimate of Disability
OBJECTIVE ANATOMICAL SCARS OR DEFECTS	100	— Alertness, acute perception. — Distinguish moving objects.	QUICKNESS 10	{ Slower in extremity activity and technical requirements }	{ 1% of 10 is % disability }
SORENESS, TENDERNESS, SWELLING, INFLAMMATION	90	— Facility balance, equilibrium, syn-chronizing eyes with extremities.	COORDINATION } 20	{ Awkward, clumsy mis-judgment. Loss of technical ability }	{ 1% of 20 is % disability }
MUSCLE AFFECTION FIELD OF VISION	80	— Dexterity, skilled observation.			
REFRACTORY CHANGES, COLOR DEFECTS	70	— Clearness, distinct perception, dependability, recognition.			
CENTRAL CHANGES	60	— Differentiation, accommodation.	STRENGTH 20	{ Encumbrance mistakes, difficulty recognition }	{ 1% of 20 is % disability }
PARALYSIS REFLEXES	50	— Accuracy, surety for leg and arm action. Precision minuteness.	SECURITY 10	{ Perplexity, uncertainty, variation, caution, nervousness }	{ 1% of 10 is % disability }
MALFORMATION	40	— Concentration, tolerance,			
OPHTHALMOSCOPIC FINDINGS	30	— Consistency in technical details	ENDURANCE 20	{ Inattention, strain, exhaustion }	{ 1% of 20 is % disability }
	20	— Circumspection, caution, defense, quick resistance.	RISK 10	{ Reckless. At-tempt to work in dangerous position }	{ 1% of 10 is % disability }
	10	— Sound appearance, noticeable defect or inaccuracy.	PRESTIGE OF NORMAL PHYSIQUE } 10	{ Averse influence of obviously impaired eye function }	{ 1% of 10 is % disability }
	0	—			

loss of motion in a joint does not limit the part to 50 per cent. of its normal functional capacity.

In attempting to base the disability upon the loss of earning capacity or wage loss, the physician will meet with many complications involving questions entirely without his sphere. Readaptability, age, possibility of occupation, experience, training, mentality and willingness to try, are all involved.

How then can the physician measure a man's disability? The only solution is for him to cling to his clinical training and fundamental scientific knowledge of the human organism, because only one who is trained in medical science can explain the factors which influence physical fitness and functional ability. When the extent of physical damage to the anatomy of the organism and the resulting physiological changes have been estimated, then the industrial court may be in a position to relate the economic factors and establish a ratio of loss to social environment.

The method devised by the writer, and published in the *Journal of Surgery, Gynecology and Obstetrics*, February 15, 1933, seems to furnish a satisfactory basis for rendering an opinion as to the extent of disability. It provides a measuring device for translating physiological alterations into percentage of loss of functional ability relative to ordinary manual labor. The method of analysis is based on the determination of the percentage of loss of each of the fundamental factors which would limit the person in performing the duties of an ordinary manual laborer.

These factors have been summarized in seven divisions, five of which are strictly physiological and two of which are related to industrial expectation. It is necessary that each of the factors of normal function be given an evaluation according to its importance to 100 per cent. normal working capacity. When this is done the percentage of loss of each factor will give the total per cent. of disability.

The writer has arbitrarily set these values as follows:

This is outlined in Chart No. I. Similar charts for deducing the degree of disability can be made for the body as a whole or for specific parts of the body. Charts Nos. II, III, and IV, demonstrate how this may be done for the arm, leg and eye.

In estimating the extent of disability, all pathological conditions

CHART NO. IV. EVALUATION OF EXTENT OF DISABILITY
in the eye

Clinical Findings	Measuring Rod of Function	Factors of Function	Value of Factors	Factors in Loss of Function	Estimate of Disability
OBJECTIVE ANATOMICAL SCARS OR DEFECTS	100	— Alertness, acute perception. — Distinguish moving objects.	QUICKNESS 10	{ Slower in extremity activity and technical requirements }	{ 1% of 10 is % disability }
SORENESS, TENDERNESS, SWELLING, INFLAMMATION	90	— Facility balance, equilibrium, synchronizing eyes with extremities.	COORDINATION } 20	{ Awkward, clumsy misjudgment. Loss of technical ability }	{ 1% of 20 is % disability }
MUSCLE AFFECTION FIELD OF VISION	80	— Dexterity, skilled observation.			
REFRACTORY CHANGES, COLOR DEFECTS	70	— Clearness, distinct perception, dependability, recognition.			
CENTRAL CHANGES	60	— Differentiation, accommodation.	STRENGTH 20	{ Encumbrance mistakes, difficulty recognition }	{ 1% of 20 is % disability }
PARALYSIS REFLEXES	50	— Accuracy, surety for leg and arm action. Precision minuteness.	SECURITY 10	{ Perplexity, uncertainty, variation, caution, nervousness }	{ 1% of 10 is % disability }
MALFORMATION	40	— Concentration, tolerance, consistency in technical details			
OPHTHALMOSCOPIC FINDINGS	30	—	ENDURANCE 20	{ Inattention, strain, exhaustion }	{ 1% of 20 is % disability }
	20	— Circumspection, caution, defense, quick resistance.	RISK 10	{ Reckless. Attempt to work in dangerous position }	{ 1% of 10 is % disability }
	10	— Sound appearance, noticeable defect or inaccuracy.	PRESTIGE OF NORMAL PHYSIQUE } 10	{ Averse influence of obviously impaired eye function }	{ 1% of 10 is % disability }
	0	—			

FIG. 5



Final result in ankylosis of the elbow: extension and flexion limited to an arc from 170 degrees to 90 degrees. What is the permanent disability estimate?

out such duties as reaching, pointing, holding, pushing, pulling, striking, carrying, swinging, throwing, turning, and lifting. The relative loss of accomplishment of these duties as indicated through disturbances in quickness of action, coordination, strength, endurance, security, safety, and prestige of normal physique, will vary according to the position of ankylosis. From the standpoint of industrial occupation, many factors might influence the loss of ability to carry out certain duties, particularly since the hand and arm enter into so many forms of skilled trades.

Since the range of motion from 180° to 90° includes the greater portion of the requirements for accommodation of the hand and arm for all kinds of occupations, only the extreme requirements of finer movements are handicapped. From the standpoint of quickness and coordination, such acts as turning, twisting, throwing, striking, reaching and lifting will be especially limited.

Possibility of compensatory adaptation.—Possibilities of rehabilitation and compensation render a very great variation in the prognosis as to what the limitation in earning capacity and working ability eventually may be. In respect to the elbow, the more the limitation approaches 180° the less the ability to compensate to all general influences, yet the less time it will require for adaptation, because only the heavier type forms of labor can be performed. When the person has been trained at only the heavier forms of duty and his elbow becomes limited to a range less than a right angle, the period of adaptation will require a longer period for re-education to the finer and more skillful occupations. In the case of A, since he has a range of motion in the arc most generally useful to the use of the arm, the possibilities of adaptation are extremely favorable.

In making up our estimate in terms of percentage after consideration of the foregoing facts, we turn to Chart No. III and place, what in our opinion is the percentage of loss, opposite each functional factor. For example:

Loss due to delayed action.....	25%
Loss due to awkwardness.....	25%
Loss due to weakness.....	15%
Loss due to insecurity.....	15%
Loss due to diminished endurance.....	15%
Loss due to increased risk.....	10%
Loss due to averse influence to employment.....	15%

The total percentage of disability would be estimated as follows:

25% of 10 (value of quick motion factor).....	2.0
25% of 20 (value of coordination factor).....	5.0
15% of 20 (value of strength factor).....	3.0
15% of 10 (value of security factor).....	1.5
15% of 20 (value of endurance factor).....	3.0
10% of 10 (value of safety factor).....	1.0
15% of 10 (value of physique factor).....	1.5
Total.....	<u>17.5%</u>

THE CRIPPLED HAND

By ISIDORE COHN, M.D., F.A.C.S.

Associate Senior Surgeon, Touro Infirmary; Professor of Surgery, Graduate School of Medicine, Tulane University, New Orleans, Louisiana

WHAT is more necessary than a hand which functions perfectly?

This question prompted a review of my own experience, some of which indicates that the importance of this function is often overlooked.

While preparing this paper a patient, illustrating all of the points I wish to bring out, presented herself for examination. Briefly, the story is as follows:

The patient met with an automobile injury several months before. The wounds were sutured by the first available doctor. Healing proceeded slowly. At the present time the patient has a crippled hand—there is loss of sensation and atrophy of all of the muscles of the hand, palm and fingers. There is glossiness of the skin and loss of the power of flexion in the fingers and wrist and of all other useful functions. At the present time her hand is ornamental only when covered by a glove.

What a different picture might have been presented if a knowledge of anatomy had been applied? It is true that there would be no need for telling this sad story—there would be no crippled hand and no need for a secondary operation, prolonged aftercare, and doubtful result.

Experience with cases like this indicates that more attention should be paid to what may properly be called preventive surgery, that is, surgery which is calculated to prevent or minimize economic loss. In the treatment of wounds the principles of preventive surgery should be regularly applied. The treatment of the average wound is considered too trivial to warrant the attention of a senior surgeon, and the interne in the hospital would consider it a reflection on his ability if he were not allowed to proceed unsupervised in the management of these cases.

Let us ask ourselves just what happens:

When a wound is seen do we try to visualize the anatomic structures which may have been injured?

Are these cases immediately examined to determine the loss of function which may be due to muscle, tendon or nerve injury?

Are these wounds debrided as a rule?

Is it a routine practice with those who see lacerated, incised or punctured wounds to do more than suture the wound?

Is much thought given to the use of the particular suture material best adapted to the kind of tissue involved?

The answer to these questions, I think, is in the negative.

If we do not know the exact condition then how can we expect to prevent disability?

Careful attention to details of diagnosis and meticulous application of surgical principles characterizes a surgeon who is desirous of shortening disability and of obtaining a primary cure. The opposite are the characteristics of the operator who is only treating another case and whose one desire is to finish the job for obvious reasons chiefly remunerative.

Kanavel has done much within recent years to direct interest to the important subject of infections of the hand.

In the present review I will consider only trauma as a factor in the production of the crippled hand. Trauma, with or without wounds, often causes crippling defects of the hand. Trauma at a distance is of importance because the nerve injury produces paralysis and atrophic muscular changes. Since this is true we must keep constantly before us the origin of the brachial plexus and the distribution of the important nerves which are derived from the plexus. Stretching of the plexus or severance of one of its trunk or major branches is associated with definite and characteristic sequelae too often overlooked until the late manifestations are well developed. In order to avoid criticism the original notes should include both negative and positive evidence with reference to possible nerve injury.

It may be argued that time does not permit careful investigation immediately after the accident. This is not an acceptable answer. Time consumed in this manner will avoid many delayed operations and much entirely unnecessary physiotherapy.

Patients on whom the primary nerve damage has been over-

looked are often done the injustice of being discharged as cured, the doctor being under the impression that the patient is a malingerer. If the patient happens to be a compensation case the question of refusal to pay compensation may work a hardship on the patient if his disability is bona fide.

Atrophic changes, sensory disturbance and loss of muscle power should direct our attention to nerve injury. Prompt treatment, directed to this phase of the situation, will shorten the period of disability.

The exact location and nature of the damage must be determined and it requires patient effort to decide whether there has been stretching or severance of one of the cords or trunks of the plexus.

The need for accurately determining the location and the extent of the injury before beginning treatment is one of the essential factors in handling these cases. It may be pointed out here that this requires only one thing—a careful examination and coordination of the findings with normal anatomic distribution of the nerves in question. To many of us it serves as a reminder that anatomy which seemed so dry when at school is nevertheless of inestimable practical value.

Operative surgery directed towards the relief of nerve injury is but a well conducted dissection, plus the application of certain technical details in an aseptic field.

There are some technical points to remember if a case proves to have a severed nerve, and suture of the nerve is to be done. Aseptic technic must be scrupulously observed; hemostasis must be as nearly complete as possible; and there must be as little trauma as possible to surrounding tissue, as nerves readily become enclosed in scar tissue. The most satisfactory way to prevent this is to have the muscle bed in which the sutured nerve is left as nearly untraumatized as possible. Whether to use a tourniquet is matter of personal opinion. If a tourniquet is used care must be exercised that it is not left on too long. Pressure paralysis may result. Methods of preventing adhesions by the use of fascia, segments of veins and other material have not proved uniformly successful. The suture should penetrate the nerve as little as possible. Fine silk is the most satisfactory material. There should be no tension on the suture line.

Positions that will relieve any possible tension are desirable. Flexion of the elbow to a right angle, and immobilization in that position is most often desirable.

Roentgen ray pictures taken following accidents in which no fracture is evident cause some surgeons to make the erroneous inference that only a contusion has occurred, and a possible nerve or muscle damage is entirely overlooked.

The late roentgen ray appearance due to disturbance or circulation and innervation is often misinterpreted. Decalcification and other atrophic changes may well be the result of circulatory and nerve damage.

In order to illustrate the foregoing statements, all of which are based on actual experience and not on hypothetical cases, the following brief summaries are introduced.

CASE 1.—Mrs. F. age fifty-four years. Diagnosis: Stretching of Brachial Plexus. Injured right shoulder April 29th, 1932. She was continuously under the care of a doctor from the time of the accident. The attending physician believed that the patient was a malingerer. However, because the patient persistently stated that she had pain, and because she was unable to abduct her arm and to grasp objects, I was asked to see her. At the time of my examination I found slight atrophy of the shoulder girdle and the forearm. There were color changes in the palm of the hand and limitation of abduction. If the arm was abducted beyond sixty degrees the extremity would drop when support was removed. The muscles of the arm and forearm were flabby. Sensation was diminished "everywhere" on the right arm below the clavicle. The grip was not as good in the right hand as in the left.

From these findings it seemed evident that the patient was suffering from a brachial plexus injury, probably stretching. The patient was totally incapacitated for her occupation. Following treatment she was finally restored to earning capacity.

Reviewing this experience we find that there are several interesting factors which may be of service when similar episodes occur in practice.

You will note in this particular case that because of the roentgen ray, which was negative for fracture, the inference was drawn that nothing except a contusion of the shoulder had occurred. Subsequent events proved that this conclusion was unwarranted.

The atrophic changes and sensory disturbance should have directed the attention of the attending physician to nerve damage.

Prompt treatment directed to this phase of the case would have shortened the period of disability.

A similar but more serious disability is illustrated by the next case.

Mr. E. J. J., age seventy-six years, suffered a "dislocation of the shoulder" May 20th, 1929. Reduction was done by his attending physician and the arm bandaged for seven days. The patient came under my observation July 20th, 1929.

At the time of my examination he stated that he had been "unable to elevate the wrist (by this the patient meant dorsi flexion) since removal of the bandage."

On examination we found an apparent elevation of the left shoulder. There was a depression just below the clavicle. There was limitation of abduction. Edema of the arm. Atrophy of the muscles of the arm, and limitation of extension and flexion of the elbow. There was loss of dorsi flexion and extension of the fingers.

The treatment resorted to was conservative, believing the condition to be due to stretching of the plexus.

Comments.—Here we find an elderly man with complete loss of the useful functions of the right hand and arm following a simple injury, a dislocation of the shoulder. The drop wrist, which should have indicated to the attending physician nerve damage, was evident as soon as the primary dressing was removed. No attention was paid to the condition. Rheumatism was supposed to be the cause. Even the roentgen ray interpretation failed to be impressive to some as late as the time I first saw him. From the roentgen ray report I quote "the changes are considered to be typical of an infectious arthritis" in spite of the fact that the radiologist noted that the carpal bones were "almost completely decalcified". With the history of an accident, a drop wrist and atrophic changes in the soft tissues, decalcification might very properly have been attributed to a disturbance in innervation.

The exact location and nature of the damage required careful study of the signs and symptoms present. In this instance there was flattening of the shoulder, the space between the acromion and the head of the humerus seemed to be increased, there was wrist drop and the deltoid did not respond to galvanic stimulation.

The above facts indicated that the posterior cord was injured above the origin of both the musculo spiral and the circumflex. (The circumflex supplies the deltoid.)

The outer cord of the plexus could be eliminated because all muscles supplied by the musculocutaneous (coracobrachialis, biceps and brachialis anticus) and those supplied by the external thoracic (pectoral muscles) responded to galvanic stimulation. There was nothing to indicate disturbance in the median or ulnar distribution.

It was important to determine whether there was severance or stretching. This differentiation meant the adoption of either conservative methods of treatment or operative intervention.

We concluded that there was stretching rather than severance of the posterior cord because the extensors of the forearm (extensor carpi radialis and anconeus as well as the triceps) responded feebly to galvanic stimulation.

Since we considered this to be due to stretching, conservative treatment consisting of electrical stimulation, massage and gradual stretching of contracted muscles together with active exercise was instituted.

After nearly a year under a conservative plan of treatment this patient was sufficiently recovered to attend to his ordinary duties.

The two cases thus far mentioned illustrate sufficiently the crippling effect of unrecognized plexus injuries which are not severe enough to cause severance.

INJURIES ASSOCIATED WITH SEVERANCE OF NERVES

In injuries which are followed by persistent anesthesia, atrophy, or other evidence of nerve damage, the location of the site of injury is the essential thing before surgical repair is attempted.

Illustrative of this statement the following cases are cited:

CASE 3.—Mr. M. S., age twenty-four years. Diagnosis: Brachial Plexus injury. A tree fell on patient March 6th, 1923, four months before I saw him. Immediately following the accident he was unable to use his right arm and forearm. The only movements which remained were palmar flexion of the hand and fingers. Dorsi flexion was lost. There was loss of sensation of pain, touch, heat and cold over the right shoulder, lateral aspect of the arm, back of forearm and dorsum of the hand and fingers. Sensation remained on the palmar aspect of the fingers, the flexor surface of the forearm and inner surface of the arm. Abduction of the arm was limited. Rotation of the shoulder was not impaired.

On examination, July 8th, 1923, I found complete loss of motion of the right arm, forearm and extension of the hand. He was able to flex the hand a little, could move the fingers some. There was loss of all reflex in the right upper extremity. Loss of all sensation over the right shoulder, lateral surface

of arm, exterior surface of forearm, dorsum of hand and fingers, and the right thumb. There was slight atrophy. All sensation was present over the palmar surface of the fingers, flexor surface of forearm and inner surface of axilla.

It will be seen from the results of the examination that the middle trunk of the brachial plexus was severed since not only the musculospiral but also the circumflex and the musculocutaneous nerves were involved. This combination could only be due to injury of the middle trunk or the outer and posterior cords separately.

At the time of the operation I found the middle trunk severed. Suture was done and the patient had regained some use of the arm when last seen.

Having briefly presented the foregoing case which involved plexus injury I will now direct your attention to injuries involving a single nerve.

CASE 4.—Mr. D. G., age twenty years. Diagnosis: Musculocutaneous nerve severance following automobile accident. Suture five months after the accident. Perfect restoration of function.

Automobile accident May 28th, 1932. He was treated within two hours of the accident in a hospital. According to his statement he was told that no fractures were found. No roentgen rays were made. His complaints, November 5th, 1932, were "at the present time my left arm seems to be getting smaller. There is loss of power in my arm. My hand seems to be all right. I cannot pull like this (the patient demonstrated flexion of the elbow)." He further stated that his grip was not as good as prior to the accident. He had noted some numbness on the outer side of his left forearm.

On examination we found "an oblique scar on the anterior aspect of the left arm, upper limit of scar on level with the lower limit of the axillary fold. The scar is three inches long, about one-eighth inch wide. The left arm is smaller than the right below the attachment of the deltoid. There is marked difference in the contour of the two arms, the left arm is almost straight below the middle third. The left forearm is smaller too, particularly over the outer side, the supinator group. I believe there is some atrophy of the fingers. In fact the fingers are all smaller on the left hand than on the right. Some atrophy of the thenar region. There is a difference in the color of the palm of the hands, left not as deep as the right, and there is some pallor on the dorsum of the left hand when compared with the right. The right forearm when looked at from the dorsum does not seem to be as deeply pigmented and is smaller. When comparing the two arms by palpation there is a marked flabbiness of the muscles of the left arm below the deltoid. The biceps seems much smaller on the left than on the right, and the triceps is flabby. I get the impression that there has been an absorption of some of the subcutaneous fat. The muscles of the forearm are flabby on the left as compared with the right side."

"The grip in both hands is excellent. Abduction, left arm, is not limited. Rotation of the shoulder not limited, but against resistance he does not abduct the left arm with the same ease that he does the right. Resisted flexion of the elbow shows a marked difference in the two, the left is much weaker. Extension of the elbow against resistance is not as limited as flexion on the left side."

"There is an area of numbness on the inner side of the middle third of the arm and over the radial side of the upper two-thirds of the forearm, a narrow strip of numbness."

The patient was referred to the Department of Physiotherapy and their report coincided with our clinical findings,—the examination indicated a musculocutaneous nerve injury.

Comment.—This patient was seen by a physician immediately following the accident. The wounds in the soft tissue had been meticulously sutured and the *nerve injury entirely overlooked*. For five months the condition progressively became worse. If an attempt had been made to determine, at the time of the accident, evidence of nerve injury by testing for loss of function and sensation, months of disability and a secondary operation would have been avoided. When the patient finally came under observation a musculocutaneous injury was clearly indicated, either a severance or an inclusion in scar tissue. There was atrophy of the biceps and brachial, limitation of voluntary flexion and anesthesia on the radial side of the dorsum of the forearm. There was atrophy of the thenar region and color changes in the palm.

At operation exposure of the musculocutaneous nerve above and below the site of the injury revealed the severance of the nerve and scar tissue enclosing the ends. Operation consisted of excision of the ends, removal of scar tissue, flexion of the elbow to diminish traction and at the same time to make approximation of the severed ends easy. We were able to suture the approximated ends with fine silk. Care was exercised to avoid tension on the suture line and to obtain a careful hemostasis. A plaster cast with the elbow flexed at right angles was applied.

As soon as possible following the operation treatment with interrupted galvanic and sinusoidal current was begun.

Three months after operation the biceps had developed remarkably. All functions had returned and only a small area of anesthesia remained on the dorsum of the forearm. The "grip" had returned and the boy was eager to resume his normal activities.

CASE 5.—Miss E. Mc., age nineteen years. Diagnosis: Median nerve injury. On July 12th, 1915, she fell through a glass door and cut her right forearm just above the wrist. Following the accident she was immediately treated. The treatment consisted of controlling the hemorrhage and suturing the superficial wound.

At the end of the fifth week the patient came to the surgical clinic of

Touro Infirmary. She complained of loss of sensation and an inability to stretch out the hand. Examination showed marked atrophy of most of the fingers, the palm, and the thenar and hypothenar areas. There was glossiness of the skin of the palm, and some cyanosis and loss of sensation in the thumb, index, third and fourth fingers. She could not stretch her hand beyond a right angle. It was thought advisable to operate to relieve the condition.

"Operation, August 31st, 1916. Median nerve was exposed under local anesthesia after which the field of the old injury was explored and found that the median nerve was surrounded by scar tissue. The tendon of the palmaris longus was found cut as well as the flexor tendon of the index finger. The nerve was liberated from the scar tissue and the tendons sutured."

At the end of the second month she was able completely to extend the wrist. Improvement was steady until about September 1916, at which time it was noticed that there was considerable swelling under the scar. After consultation I decided to operate again. This operation was done April 11th, 1917. Under general anesthesia the median nerve was exposed; a neuroma was found and excised. The ends were approximated with silk sutures. A molded plaster splint was applied to the dorsum of the forearm and hand with the wrist in palmar flexion.

The wound healed without interference and on May 18th she had complete return of sensation of pain and touch, sensation of hot and cold was not yet as marked as that of touch and pain. She received electrical treatment from Dr. Van Wart.

Notes made at a later date state that she "used the typewriter without difficulty. Grip gradually improved. At present almost as much muscle power in right hand as in the left. She returned to her former occupation as a telegraph operator."

CASE 6.—Mrs. S. G., age thirty-five years. Diagnosis: Median and Ulnar Nerves severance; secondary atrophic changes; tendon severance. Patient was in automobile accident December 11th, 1932. The right arm went through the glass window. Accident happened fourteen miles from town. A member of the party applied a tourniquet immediately. It required only about twenty minutes for the patient to arrive at a hospital. During that time she made no effort to move her fingers, so she does not know the exact extent of loss of function. Repair was instituted at once. *A splint was applied with the hand in complete extension.*

In the interim the patient has been under the care of another physician through whose courtesy I had the opportunity to examine her. The following notes were made at the time of my examination, March 1st, 1933.

"The right hand is in a position of palmar flexion of about 130 degrees, slightly deviated to the radial side. There is a marked difference in the color of the two hands, the right, particularly on the dorsum, being of a violaceous hue. The creases on the dorsum of the hand at the interphalangeal fold have disappeared below the folds 1 and 2. The discoloration of the fingers is greatest below the first phalanx."

"On the volar aspect of the forearm there is an irregular scar beginning about the junction of the middle and lower third of the forearm and extending down $2\frac{3}{4}$ inches, and there is also an irregular transverse scar which meets the lower limit of the linear scar making approximately a T. Above the level of the

scar the color of the arm is very different from the color below it. There is atrophy in the thenar and hypothenar areas, glossiness of the skin of the fingers and discoloration is more marked on the flexure surface than on the dorsum. The thumb is adducted."

"The hand is cold and dry. Patient is not able to flex the wrist further than about 11 degrees. Dorsi flexion is not possible beyond the midline. Any attempt to get further than the normal position causes a flexion of the fingers at the interphalangeal joint, and the patient is evidently conscious of stretching of the muscles. Supination of the right forearm is associated with rotation of the shoulder."

"Patient is unable to distinguish between hot and cold, or between a blunt and a pointed instrument, over the flexure surface of any of the fingers. On the dorsum of her fingers there is some sensation; she is able to distinguish between hot and cold everywhere on the little finger, and on the ulnar side of the ring finger down to the interphalangeal joints 1 and 2 and on the first phalanges of the index and middle fingers, but on the middle and terminal phalanges she says she is unable to differentiate between hot or cold, or between a blunt and a pointed instrument."

"No grip. She is unable to flex more than one-third the normal range of the interphalangeal joints 1 and 2. There is no flexion at the metacarpophalangeal joints, perhaps, just very slight flexion. Dorsi flexion of the wrist is limited, apparently an extra-articular affair rather than an intra-articular one."

"Palpating over the scar I am able to feel the radial pulse, but just to the ulnar side of the radial artery there is a cord-like mass. There is discharge from the wound at the present time."

The patient was referred to the Physiotherapy Department and the report from that Department corroborated our findings that there was a medium and ulnar nerve injury.

This patient is to be operated upon at a later date.

The cases cited serve to emphasize the need of applying the most meticulous care in the handling of what might be considered trivial wounds if we would minimize or prevent disability. Recognition of nerve injuries and immediate attention to them will redound to the credit of the surgeon and the benefit of the patient.

These statements are afforded ample proof by the following experience.

CASE 7.—Mr. S. C., age twenty-eight years. Diagnosis: Severance of Median Nerve and Flexor Tendon. Patient was admitted to Touro Infirmary November 15th, 1930, after having been seen in the Emergency Clinic. I was called to examine him, and obtained the history that he had cut the palm of his hand with an oyster knife. The doctor who had seen him on his admission to the hospital had found a small transverse incision in the middle of the palm and had noted that the patient was unable to flex his ring finger. When I first saw him, in addition to the loss of flexion of one of his fingers, I found also that there was loss of sensation of pain and touch in the distribution of the median nerve beyond the site of the wound.

Operation was immediately performed. An incision about three inches long, the middle corresponding to the transverse incision of the original wound. The extent of the incision was from the point midway between the thenar and hyperthenar eminences down to the interdigital fold. Immediately we saw the muscle belly severed in the palm and the severed ends of the median nerve were easily identified. They were sutured with fine black silk. The muscle was sutured with fine silk, a Bunnell type of suture being used. The fat was approximated first and then the skin, and the wrist put up in palmar flexion. A molded plaster splint was applied to the dorsum of the forearm and hand.

On December 5th, 1930, the following notes were made. "Return of sensation as low as interdigital fold. He is able to localize the prick of a pin as far as the interphalangeal joints 1 and 2. The patient is not able to localize pain on radial aspect of middle and ring fingers. Patient is able to flex the middle finger much better than the ring finger. There is some flexion of the ring finger but not very much.

On January 2nd, 1930, there was complete restoration of sensation of pain and touch. He was able to flex the middle and ring fingers incompletely. There was neither glossiness of the skin nor atrophy of the tissues of the fingers.

Comment.—In this instance there was an insignificant wound, yet the examination indicated serious involvement of the median nerve and flexor tendon. If a hurried routine treatment had been followed the extent of the injury would not have been known until a later date. However, the examination did include an effort to determine the extent of the injury and treatment was immediately instituted to prevent prolonged disability and a permanent crippling defect of the hand. Immediate operation restored this man's hand to its former usefulness.

In the discussion thus far attention has been devoted entirely to the crippling effects following nerve damage. It is obvious that all such cases do not receive adequate treatment.

Improvement in results can only come from carefully performed operation based on a knowledge of the primary damage.

In the time allotted to such a paper the entire subject cannot be covered. In a subsequent paper the crippling effects following severance of muscle bellies and tendons, and those due to loss of substance will be discussed.

The purpose of this presentation would not be enhanced by prolonging the discussion. My object here is a plea for more careful primary examination so that an accurate diagnosis will be followed by adequate treatment. In this way much time and disability will be saved.

Recent Progress in Obstetrics and Pediatrics

THE TOXEMIAS OF LATER PREGNANCY

By NICHOLSON J. EASTMAN, M.D.

Professor of Obstetrics and Gynecology, Peiping Union Medical College,
Peiping, China

FROM the viewpoint of etiology the toxemias of pregnancy remain to-day the same illusive enigma which they were ten or twenty years ago. Our persisting ignorance of the cause of these conditions has proved a grave handicap in their management, precluding the possibility of scientific classification and specific therapy. It has not, however, altogether prevented progress. Indeed, if one compares our modern conceptions of the toxemias of pregnancy with those of just a decade ago, he will find in this field many noteworthy advances. It is true, for the most part, that these advances are not of a fundamental nature; they are concerned little with etiology and do not attempt to postulate theories. Rather, they are of a practical character. They comprise chiefly bed-side observations, follow-up studies and statistical analyses of large series of cases. At their best they illustrate nicely what may be accomplished by the nosographical or descriptive approach to disease processes, in which the close observation of the patient's symptoms and clinical course forms the basis for conclusions.

It is the purpose of this review to consider some of the more conspicuous of these advances, attention being limited to the toxemias of later pregnancy.

CLASSIFICATION

During the eighteenth century attempts were made by several authors to group all known diseases into classes, orders and genera, just as the natural scientists at that time were engaged in arranging plants and animals in a perspicuous system. One of the best known

of these disease formularies, or nosologies, as they were called, was that of Sauvage published in 1763. In this work the author enumerated in all 2400 different kinds of disease; they were divided according to botanical custom into classes (10 in all), these latter into orders (40 in all) and the orders again into genera, the first class alone containing 78 genera. The nosology of Sauvage was widely imitated with the result that many such works appeared. These classifications of disease were based upon symptoms only and, of course, made no mention of underlying causes, which at that time were unknown. As might be expected, these cumbersome catalogues were unsatisfactory and short-lived. Not until the pathological, bacteriological and chemical researches of the nineteenth century had established the basic causes of disease, was a rational classification possible.

Our present-day classifications of the toxemias of pregnancy, like the nosologies of the eighteenth century, are based solely upon symptoms and clinical course, and are correspondingly inadequate. The classification which will be followed in this review was recommended by Stander and Peckham in 1926. It groups the common toxemias of later pregnancy as follows:

1. Preeclampsia.
2. Eclampsia.
3. Low reserve kidney.
4. Chronic nephritis in pregnancy.

The distinguishing feature of this classification is that it sharply limits the group designated as "preeclampsia" to those cases of toxemia in which an eclamptic outbreak seems actually imminent. *The clinical picture of preeclampsia, as thus interpreted, is almost identical with eclampsia except that convulsions and coma are absent.* Rapidly ascending blood pressure, increasing edema (particularly facial), substantial amounts of albumen in the urine, visual disturbances and headache, are the outstanding signs and symptoms of the preeclamptic state; it is characterized further by the fact that these alterations usually return to normal after the birth of the child. By restricting the term "preeclampsia" to these potential eclamptics, a large group of cases, hitherto classed with pre-eclampsia under such heading as "preeclamptic toxemia," are excluded and

fall into a group by themselves. These latter cases are characterized by their mildness. Thus, the blood pressure of such patients approximates, as a rule, 150 mm. Hg. systolic and 90 diastolic, while the amount of albumen in the urine is never very great, varying between a fraction of a gram and two grams per liter, the lower figures being the ones usually observed. The mild hypertension, as well as the albuminuria, disappear during the puerperium. The condition is further characterized by the fact that in subsequent pregnancies, the patient's condition does not become aggravated and her cardiovascular-renal system shows no evidence of permanent damage. *These mild, transient toxemias of pregnancy are designated under this classification as "low reserve kidney."* In other words, Stander and Peckham have thought it advantageous to divide that large group of cases, heretofore called "preeclamptic toxemia," into two groups, the one embracing cases which are actually preeclamptic, the other cases in which the process is so mild that it rarely eventuates in eclampsia. When defined in this manner preeclampsia becomes an uncommon condition, low reserve kidney an extremely common one. Among 606 cases of toxemia of later pregnancy observed at the Johns Hopkins Hospital, 323, or approximately, one-half, were classified upon discharge as low reserve kidney, while only forty-six cases, or seven per cent, were considered to be preeclampsia. Thus, low reserve kidney was encountered seven times as frequently as preeclampsia.

"Low reserve kidney" is a newly coined term which was advanced by Stander and Peckham at the time their classification was proposed. This fact, together with the great frequency of this mild condition, has caused low reserve kidney to overshadow other aspects of the classification. This seems to the writer unfortunate, since he considers that the most valuable feature of the classification is not the conception of low reserve kidney, but the introduction of a new and more precise definition of preeclampsia. When the latter term is restricted to cases in which eclampsia seems imminent, preeclampsia is a clear-cut clinical entity, is probably analogous both etiologically and pathologically to eclampsia and calls for a category of its own. The separation of these cases into a distinct group, furthermore, aids materially in establishing their prognosis and treatment.

Preeclampsia, then, may be said to comprise a small and fairly distinct class of cases. After the segregation of this entity, the mild toxemias which remain for consideration and which have been called "low reserve kidney", form a rather obscure group. Most of them show slight, temporary hypertension only; a small number of these patients suffer chiefly from albuminuria and suggest, perhaps, a very mild form of nephrosis; in others, what purports to be a transitory condition turns out to be a chronic arteriosclerotic one and has subsequently to be reclassified as chronic nephritis; in still others, after pursuing at first a mild course, the process gradually, or suddenly, becomes worse so that the picture becomes one of preeclampsia. The confused identity of this group of cases is clearly shown by the report of Peckham and Stout, published in 1931; these authors followed 190 patients upon whom the diagnosis of low reserve kidney had been made *two weeks postpartum* and discovered, when they examined the same women four to twelve months later, that the original diagnoses were wrong in approximately one-fourth of the cases. To devise an ideal designation for this diverse group of cases, is at present impossible. When the term "low reserve kidney" was introduced, its sponsors realized that it was inadequate and provisional; and they have repeatedly emphasized the fact that precise nomenclature in the toxemias will be possible only when their etiology becomes known. It seems altogether probable that the condition, "low reserve kidney", has nothing to do with the kidney and, if it has, does not depend on an actual depletion in this condition. In one typical case of low reserve kidney, studied by the author, death occurred during pregnancy from an extraneous cause and at autopsy the kidneys showed no pathological changes, either gross or microscopic. On the other hand, women who have had nephrectomies usually go through pregnancy without evidence of "low reserve kidney" or other toxemia.

In view of the confused state of our knowledge concerning low reserve kidney, the question naturally arises as to whether this new classification is worth while at all. As has already been indicated, it is the writer's opinion that the segregation of cases of true preeclampsia into a separate group is a rational step of considerable practical value and alone justifies the classification. It is true that the low reserve kidney group, as well as the term itself, is unsatis-

factory, but it must be remembered that the fault here lies primarily with our profound ignorance of the cause of this disorder. A phrase is often a useful, even if not always a faultless, label for a clinical condition. Since the name, "low reserve kidney", is now widely employed and since no better one has been suggested, it would appear that this term is as useful a symbol as any other for the unknown quantity it represents. It is thus, however, in an almost algebraic sense, that we are forced to construe this phrase.

The signs and symptoms of eclampsia, preeclampsia and low reserve kidney usually disappear entirely within two or three weeks after delivery. *Chronic nephritis in pregnancy, on the other hand, is characterized by the fact that certain of the abnormal signs noted during gestation, particularly hypertension, persist indefinitely after delivery, with a strong tendency to become aggravated during subsequent pregnancies.* As the name implies, this condition is characterized by its chronicity. If the patient's past medical and obstetrical history is available, the recognition of this complication is usually easy, since the history will show that she suffered from hypertension even when not pregnant and that this abnormality became aggravated during each succeeding gestation. In the absence of an adequate past history or if the latter is equivocal, the diagnosis of chronic nephritis in pregnancy must often be deferred until the puerperium is well over. Sometimes, however, it is possible to be reasonably sure of the chronicity of the process on the following grounds:

1. *Earliness of onset.*—The great majority of patients suffering from chronic nephritis in pregnancy develop abnormal signs, notably hypertension, before the seventh lunar month of gestation is completed. Eclampsia, preeclampsia and low reserve kidney, on the contrary, are not commonly met at this time (about once in twenty cases), and are characteristically diseases of the last six weeks of gestation.

2. *Retinal arteriosclerosis.*—It seems probable, on evidence which will be adduced later in this paper, that chronic nephritis in pregnancy is essentially a generalized vascular disease in the form of a widespread arteriosclerosis. The small vessels of the retina seem to be among the first to show these pathological changes and when the latter can be identified under the ophthalmoscope, they are of great

diagnostic aid. Irregular tortuosity of the smaller vessels, variations in their caliber, visibility of the walls of the small macular arterioles and arteriovenous compression point strongly to chronic vascular disease. When frank retinal exudates, either fresh or old, are present, the diagnosis of chronic nephritis is certain. In preeclampsia, by contrast, these vascular changes are not observed, the characteristic retinal finding in this condition being edema. Occasionally, indeed, the retinal edema may be so pronounced as to cause detachment of the retina. In low reserve kidney, the eye grounds are normal. The picture of the retina, therefore, is of immeasurable value in the differential diagnosis of the toxemias of pregnancy and a retinal examination, carried out by a competent ophthalmologist, should have a routine part in the examination of every toxemic patient.

3. *Age and parity.*—Chronic nephritis in pregnancy is met most frequently in older women and in multiparae. The average age of patients suffering from this condition is possibly thirty years, while about 80 per cent. of the cases occur in multiparae. On the other hand, of course, eclampsia and preeclampsia are characteristically diseases of young primigravidae.

The fact that it is sometimes impossible to classify cases of toxemia until several months postpartum, the frequent difficulties encountered in differentiating border-line cases and the general obscurity which shrouds these diseases, has caused some obstetricians to regard the whole procedure of classification as impractical and futile. What possible value, they ask, can a diagnosis have, when it is made many months postpartum, after the disease and the clinical problems it presented, have long ago become things of the past? The only practical way to classify the toxemias of pregnancy, they claim, is to divide them into two easily recognized groups; those with convulsions and those without. This attitude is readily understandable and is deserving of much sympathy. It loses sight entirely, however, of the *two main purposes of classification*. The first of these is to augment our knowledge of the toxemias. Pending the discovery of their cause, the intensive study of *homogeneous* groups of these disorders over long periods of time and through many pregnancies, promises to be one of our most fruitful lines of investigation. To carry out this program intelligently, like cases

must be grouped together with great care, even though it be necessary to defer final classification until many months postpartum. The second purpose of classifying the toxemias is even more important for it has to do with the welfare of the patient in subsequent pregnancies. Depending on their type, these diseases may have a grave bearing not only on the course of later pregnancies, but also upon the woman's health when not pregnant and even upon her longevity. It is the obstetrician's duty to his patient to define as exactly as possible the type of toxemia from which she has suffered,—even though it be many months later,—to the end that he may advise her intelligently in regard to subsequent pregnancies and future health.

PREECLAMPSIA

In 1921 Zangemeister observed that the eclamptic state was usually preceded by a rapid increase in the body weight; he reasoned that this was due to an accumulation of water in the tissues and concluded that the *immediate* cause of eclamptic convulsions were cerebral edema with resultant increase in intracranial pressure.—“Als das lange gesuchte Eklampsiegift is somit (unmittelbar) das Wasser anzusehen”.—Zangemeister showed that the normal gravida gains about a pound a week, but that in preeclampsia the gain may be as high as two pounds a day. The theory that edema of the brain is an etiological factor in the production of eclampsia, was not new, but had been advanced as early as 1864 by Traube and Rosenstein; such emphasis, however, has been laid upon it by Zangemeister that it has come to be associated with his name. Studies made during the past decade have confirmed the observations of Zangemeister and tend in general to attest the validity of this hypothesis.

For instance, Randall made an interesting comparison several years ago at the Mayo Clinic between the weight gains of normal and of toxemic pregnant women. He studied the weight records of 200 unselected primigravidae with normal pregnancies and found that the average gain from the onset of pregnancy to delivery was 23.2 pounds of which 7.75 pounds were added in the last eight weeks; one hundred multiparae showed an average gain of 21 pounds of which 5 were added in the last eight weeks. By contrast, the

average gain of 12 toxemic gravidæ was 44.5 pounds. This is not particularly significant in itself, since pregnant women may gain this much and yet follow a normal course. The pertinent fact is that 25.4 pounds were gained during the last eight weeks so that the composite weight curve for women with toxemia stood in marked contrast to that of normal pregnant women. Quite recently Siddall and Mack have studied the weight changes in 663 cases of normal pregnancy and in thirty-nine cases of toxemia of pregnancy. They confirm the fact that the average gain in weight of the normal gravida during the last sixteen weeks of pregnancy is one pound a week. In their cases of toxemia of pregnancy, the average gain during this period was 20.9 pounds as compared with 15.7 for the normals. Considering an excessive gain to be twice the normal average, the authors found that 72 per cent. of the toxemia patients gained excessively at one or more periods. There were four cases of eclampsia in the series. Each one of these patients had gained excessively at one or more periods during the previous four months; in two cases the excessive gain preceded and in two cases the gain coincided with the appearance of the first sign of toxemia.

A sudden, excessive gain in weight during the last trimester of pregnancy is now recognized as a cardinal sign of preeclampsia. Very often, when the blood pressure readings and the urinary findings of a case are inconclusive, the weight record may prove of decisive diagnostic import. Sudden gains of more than two pounds a week should be viewed with suspicion; gains of more than three pounds with alarm. Weight increases of the latter magnitude call for frequent blood pressure and urinary examinations, and if these findings are also abnormal, hospitalization with intensive treatment is usually indicated. Preeclampsia is a fulminant disease and the weight gains often far exceed the figures just cited, sometimes exceeding, as noted by Zangemeister, two pounds a day. The writer is quite aware, as emphasized by Siddall and Mack, that sudden and decided weight gains are occasionally seen in perfectly normal gravidæ, but these are not accompanied by elevations of the blood pressure or by urinary abnormalities. In any event, it seems prudent to view every sudden increase in weight with concern, for it is better to be alarmed unnecessarily once in a while than to have cases of eclampsia develop under one's eyes.

If cases of preeclampsia are studied from the viewpoint of fluid intake and output, it is at once apparent that these sudden gains in weight are due entirely to an accumulation of water in the tissues. This is probably the result of many factors, most of which are inadequately understood. An increased permeability of the capillary walls is perhaps the predominant cause. Another important factor is the marked tendency of pregnant women, particularly gravidæ suffering from toxemias, to retain salt. The studies of Rupp on this question are of considerable interest. He fed five grams of sodium chloride to normal non-pregnant women, to normal pregnant women, and to women suffering from the toxemias of pregnancy, and then investigated the resultant changes in the chlorides of the blood and urine in order to deduce the fate of the salt. In normal non-pregnant individuals, the ingestion of this amount of sodium chloride was followed by a marked rise in the blood chlorides together with a simultaneous increase in the urinary output of sodium chloride. In normal pregnant women, on the other hand, the blood chlorides augmented only slightly after feeding, while the urinary excretion of chlorides was delayed. In cases of toxemia with edema this effect was still more marked, the ingestion of sodium chloride having no effect on either the blood or the urinary chlorides, all of the ingested salt being held by the tissues. Finally, Rupp analyzed the edema fluid of these patients and showed that in cases of toxemia with edema, the ingestion of salt caused a characteristic increase in the sodium chloride content of this fluid.

The effect of large doses of salt on the water balance of the body is well known. Even in normal, non-pregnant individuals, an increased intake of sodium chloride causes water retention. A particularly convincing study of this problem has been made by H. L. White, who gave a large series of medical students various solutions of sodium chloride to drink and found that the hourly excretion of urine, thereafter, diminished in direct proportion to the amount of salt which had previously been ingested. Were a similar investigation to be carried out on women suffering from preeclampsia, we might expect even more striking results. Just such a study actually was made in 1929 by Harding and Van Wyck in the belief that the administration of sodium chloride in such cases might be a valuable therapeutic measure. These authors gave several patients, who were

suffering from various grades of toxemia of pregnancy, intravenous injections of 300 cc. of 6 per cent. sodium chloride solution. The results were well-nigh disastrous. One patient, who had received two such injections within twenty-four hours, developed a fulminating preeclampsia with dramatic suddenness and, worse still, went shortly into actual eclampsia and had three typical convulsions; meanwhile, the blood pressure had risen from 128/100 to 200/140 and the albuminuria had more than doubled in intensity. The patient recovered, but the authors write that they have no wish to continue their observations in this direction. They believe firmly that a high intake of salt, ingested at the right moment in a developing toxemia, will produce albuminuria, increased blood pressure and even convulsions in a short period of time.

The great affinity for salt which the tissues show in preeclampsia has dictated one of our most rational means of treating this disease, namely, the withholding of salt from the diet. The value of this dietary restriction is now generally recognized; Eckelt in Germany, de Wesselow and Wyatt in England, Harding and Van Wyck in Canada, and Bland and Bernstein in the United States, all advocate salt restriction from the standpoint of the water balance of the body. Stander, in his recent monograph, recommends a salt-free diet if there is marked edema present.

In Bland and Bernstein's study of salt restriction in preeclampsia, a salt-free diet was employed in the treatment of thirteen preeclamptic patients admitted to the Department of Obstetrics at the Jefferson Medical College. On admission the patients were put to bed for three days and given the regular hospital diet. The course of the disease was followed in various ways; notably, by the blood pressure, the weight, the urinary output and the sodium chloride content of the twenty-four hour specimen of urine. On the fourth day after admission the patients were placed on a salt-free diet and allowed the freedom of the ward, the above observations being continued. The blood pressure, which was high on admission, was not influenced by rest in bed on a regular house diet. The reverse was true when the patients were placed on a salt-free diet, despite the fact that they were permitted the freedom of the ward. With two exceptions, every patient showed a prompt drop in blood pressure to normal. Although the blood pressure in these two cases was not in-

fluenced, there was a decided improvement in the clinical symptoms; the edema disappeared, the body weight diminished and the albuminuria and cast excretion decreased.

While most observers, including the present writer, have failed to secure the perfect results reported by Bland and Bernstein with the salt-free diet, the measure is unquestionably a rational one and is usually followed by a marked improvement in the patient's condition. The withholding of salt from these patients is probably of greater importance than the withholding of protein. The latter dietary restriction has insinuated itself into our practice to such an extent that it is now regarded an almost inviolable dogma in the treatment of these cases. However, in so far as the ability of the kidneys in preeclampsia to excrete nitrogenous substances is concerned, this teaching appears to be largely a relic of the days when the toxemias were allied with uremia. From this point of view, real evidence for the dietary restriction of protein in preeclampsia is wanting, since these patients show no impairment of the kidney to eliminate nitrogenous substances and, even when studied by our most delicate renal function tests, excrete urea, the end product of protein metabolism in the body, with ease. In normal pregnancy, Burger has given as high as 200 Gm. of protein a day for three weeks, without noticing any unfavorable symptoms. Harding and Van Wyck have fed preeclamptic patients diets high in protein or fat but salt-free, and have found that such diets produced no aggravation of symptoms. On the contrary, their patients showed clinical improvement. Accordingly, these authors believe that ordinary hospital or home diets are entirely satisfactory in the treatment of preeclampsia, provided they are salt-free.

Dieckmann, on the other hand, in a series of valuable experimental studies, has brought evidence to bear against the employment of protein in the diets of preeclamptic patients. His stand is in no way related to the ability or inability of the kidneys to excrete nitrogenous substances in this disease, but is based on the specific dynamic action of ingested protein in increasing the coagulability of the blood, particularly the blood in the portal capillaries. Evidence that ingested protein does have such an effect has been advanced by Mills, as the result of a series of investigations. Dieckmann, by feeding dogs full meals of raw meat, and at the same time giving

them intravenous injections of placental protein, in some instances into the general circulation and in others into the portal vein, was able to produce in these animals hepatic lesions which resembled the characteristic ones of eclampsia. The liver changes were apparently the result of the increased tendency of the portal blood to clot, so that thrombi formed in the smaller portal tributaries, and these in turn caused peripheral hemorrhage and necrosis in the liver lobule. This author believes that the well-known liver lesion in eclampsia is produced by a similar mechanism. Just as chloroform is contraindicated in eclampsia because it produces liver injury, so meat is contraindicated in preeclampsia, according to Dieckmann, because it may produce an hepatic lesion similar to that of eclampsia.

The belief that dietary indiscretions, particularly a high intake of protein, may be an etiological factor in eclampsia received strong support during the World War, when it was observed that the incidence of this disease was greatly reduced in the countries affected by the so-called hunger blockade. Zangemeister made a detailed study of this question and found that for the period January 1, 1911, to June 30, 1915, the incidence of eclampsia was 1 in 70 (pregnancies), whereas during the period from July 1915 to December 1916, it decreased to 1 in 104, the statistics being based on figures from various German clinics. Hinselmann, after studying all cases reported in the literature from lying-in hospitals, concluded that the incidence before the war was 1 in 69.5 (pregnancies); during the war 1 in 118.5; and after the war 1 in 78.6. In Sweden, during 1917-1918, when there was a control of food supplies, Groene found a similar decrease in the frequency of eclampsia. While various reasons have been cited to explain this lowered incidence during the World War, the one most frequently advanced is that the women received a diet low in protein and fat, and correspondingly high in carbohydrates.

Opinions, therefore, differ concerning the importance of withholding protein from preeclamptic patients. But, whether it is completely justified or not, this restriction causes little hardship (less than withholding salt), and to-day it is generally customary in this disease to prescribe a salt-free, low-protein diet.

Dietary therapy in preeclampsia, however, is at best a temporizing measure. The treatment of preeclampsia *par excellence* is ter-

mination of the pregnancy. Most of these patients are approaching the expected time of confinement and it is usually desirable to deliver them at an early date, not only in order to thwart the onset of eclampsia but also to prevent permanent kidney damage. The question of when to take this step and how best to do it, often requires the nicest obstetrical judgment. The factors which will weigh most heavily in the decision are; the imminence of an eclamptic outbreak, the likelihood of renal injury as a result of temporizing, the size, position and viability of the child, and the operative risk involved in interference. In cases of fulminant preeclampsia (as defined in this article), Cesarean section under local infiltration anaesthesia is usually the procedure of choice. This operation should not be unduly postponed in the hope that rest in bed and medical treatment will correct this severe type of toxemia. During the past year the writer has seen two patients develop eclampsia when under such an "expectant" regime and, desirable as it is to improve the condition of the patient before operation, he believes that once the diagnosis of frank preeclampsia is clearly established, even though the patient has been observed but a few hours, immediate delivery will yield the best results. In primigravidae, in whom the disease is most commonly met, this end can be guaranteed only by Cesarean section. Margaret Basden of London has recently reported a series of thirty cases of severe preeclampsia treated by Cesarean section without a maternal death. It is her experience that the high mortality which has been shown to follow Cesarean section when eclampsia has actually supervened, does not occur when the operation is performed in the preeclamptic stage. Her usual practice in cases of preeclampsia has been to keep the patient on water only, or water, glucose and lemonade for twenty-four hours. She has found that the response to this treatment is usually satisfactory, but if at the end of that time there is only slight improvement, she induces labor. If the condition is the same or worse, she performs Cesarean section. She employs ether as an anaesthetic, but since the operation is a short one, she does not regard the type of anaesthetic as a question of great importance. This attitude toward anaesthesia is at variance with that of most American obstetricians, who feel that the type of anaesthetic may be a decisive factor in the outcome. Since ether predisposes to edema of the lung, it would seem to be contraindicated in a pa-

tient who is already water-logged. Local infiltration anaesthesia is undoubtedly the safest method and is being used more and more in Cesarean section.

Since in multiparae the likelihood of a rapid labor is much greater than in primigravidae, induction of labor is usually but not always, preferable to Cesarean section. In treating the less fulminant cases of preeclampsia, the aim should likewise be to bring the pregnancy to an end as soon as the size of the child and the condition of the mother ensure a safe outcome for both patients. If the woman is within a week of her expected date of confinement, the head engaged and the cervix not long and hard, puncture of the membranes with drainage of the amniotic fluid is an ideal method of bringing on labor. This procedure is actually one of the oldest methods for starting labor, but many years ago it fell into desuetude. Recently, the studies of Slemmons, of Guttmacher and Douglas, and of Morton, have shown that this procedure, particularly when combined with castor oil and quinine, is an exceedingly valuable adjunct to our obstetric armamentarium. A sample of the routine is as follows:

4:00 A.M.	Castor oil	30.0 cc.
5:00 A.M.	Quinine	0.3 Gm.
6:00 A.M.	Quinine	0.3 Gm.
7:00 A.M.	Quinine	0.3 Gm.
7:30 A.M.	Hot S. S. enema	
8:30 A.M.	Artificial puncture of the membranes.	

Rupture of the membranes is accomplished after placing the patient in the lithotomy position and carrying out full antiseptic toilet of the vulva as if for delivery. The first two fingers of the left hand are inserted into the cervix until the membranes are encountered. The cervix is gently stretched and the membranes stripped from the region of the internal os. A long hook, similar to one blade of a disarticulated vulsellum tenaculum, is inserted into the vagina with the right hand and guided into the cervix by the fingers of the left hand. The membranes are simply hooked and torn by the tip of the sharp instrument and as much fluid as possible allowed to run away. Usually no anaesthesia is necessary. As mentioned above, *this method should not be employed unless the patient is near her expected date of confinement, the head engaged and the cervix soft.* Under these circumstances labor will usually set in within two hours

in multiparae and within five hours in primigravidae. If these conditions are not present the line of procedure will depend upon the urgency of the indication for interference and will rest between an attempt at induction by means of castor oil and quinine alone, and induction by means of the bougie. Pituitrin should not be used in preeclampsia or eclampsia, either for the induction of labor or for the control of postpartum hemorrhage, because there is considerable evidence, as will be shown later, that the eclamptic state may be due to an oversecretion of this substance by the posterior lobe of the pituitary body. The oxytoxic principle of this gland, freed from its harmful presser and antidiuretic principles, is now available under the name "pitocin" and should be used instead of pituitrin in these cases, whenever the latter hormone is definitely indicated.

ECLAMPSIA

The late Dr. J. Whitridge Williams used to speculate occasionally upon the prognosis of the more serious obstetric complications when they occurred in women who were without benefit of medical counsel and who were forced to deliver themselves as best they could. He felt that the gravest outcome under such circumstances awaited patients with advanced degrees of contracted pelvis, while a fate almost as ominous would obtain in the severer forms of placenta previa and premature separation of the normally implanted placenta. The condition in which patients would suffer the least from lack of medical attention was, in his opinion, eclampsia.

As a result of special circumstances existing in China, the writer has had the opportunity of following, throughout their course, several cases of eclampsia in which the patients' relatives,—for reasons of their own,—refused all forms of treatment. He has seen these Chinese women lie for days in coma, suffer an untold number of convulsions, and finally deliver themselves spontaneously after the head had been in sight for hours; meanwhile, let it be remembered, these women were virtually untouched. He has followed four such cases to date and has seen four mothers survive. (Among seventy-three cases of eclampsia in Chinese women treated at this Clinic by a modified Stroganoff regime and with all the refinements of modern obstetrics, there were thirteen maternal deaths, a mortality of 17.8 per cent.)

By citing these facts, the writer does not mean to advocate a policy of therapeutic nihilism in eclampsia, but wishes simply to recall that *this disease, like many others, shows a strong tendency to spontaneous abatement, provided the patient is not killed by obstetric trauma.* From a practical viewpoint this is possibly the most important fact that has ever been learned about eclampsia. During the first two decades of this century, when the maternal mortality from this disorder ranged between 25 and 30 per cent. the cause of half the deaths was obstetric trauma, either in the form of accouchement forc   or Cesarean section. It has been shown by Peterson that the mortality from eclampsia in the United States, when treated by Cesarean section, was 26 per cent., and by Holland that the mortality in Great Britain was 32 per cent. But it may be objected that this high mortality is partly attributable to the fact that many of the operations were performed on severe cases which had failed to respond to medical treatment. That this is not the case is demonstrated by a recent collective investigation made in Great Britain, in which the cases were grouped according to their severity. As may be seen in Table I, which re-produces the results of this study, radical methods of delivery increase the maternal mortality both in mild and in severe cases of eclampsia. Similarly, the results

	Mild Cases Mortality Per cent.	Severe Cases Mortality Per cent.
(a) Natural delivery, assisted delivery or induction of labor	5	34
(b) Cesarean section	11	46
(c) Accouchement forc��	18	63

TABLE 1. Showing that radical methods of delivery increase the maternal mortality in eclampsia, whether the cases be mild or severe. (Eden.)

obtained over a long period of time at the Johns Hopkins Hospital attest plainly the danger of radical interference in eclampsia. In the early days of that Clinic extremely radical procedures were employed in this disease, and among eighty-five patients treated for ante and intrapartum eclampsia between 1896 and 1911, only two escaped operative delivery, the methods of choice being accouchement forc   and vaginal, and abdominal Cesarean section. Among a total of 110 eclamptic patients treated during this period, the maternal mortality was 22.8 per cent. Beginning in 1912 these meas-

ures were gradually abandoned and were supplanted by more conservative methods which did not aim at the immediate delivery of the patient. A transition period thus followed but since 1924 all eclamptic patients have been treated in exactly the same manner, by a modified Stroganoff regime. Among 127 cases so handled, the maternal mortality was 11 per cent., or just one-half what it had been during the "radical era."

The treatment of eclampsia to-day, then, is not concerned with the question of obstetric interference, but is simply a matter of determining the particular form of conservative therapy which is to be employed. If we may believe statistics, the exact type of conservative treatment used, seems to make little difference. In 1918, Stroganoff was able to collect from the literature 2208 cases of eclampsia, treated with morphine and chloral hydrate according to his plan, and found in this series a maternal mortality of 9.8 per cent. In 1924 Weinsenfels added 1094 more such cases, which raised the total number to 3302, of which 357, or 10.8 per cent., terminated fatally. We have already noted that the maternal mortality from eclampsia at the Johns Hopkins Hospital, where a modified Stroganoff regime has been followed, is 11 per cent. Fitzgibbon and Solomons, with the so-called Dublin treatment, have reported a mortality of 10.3 per cent. It will be recalled that this scheme of therapy consists chiefly in gastric and colonic lavage and the submammary infusion of sodium bicarbonate. Epsom salts are given after the gastric lavage and large quantities of sodium bicarbonate are used for flushing the bowels. Morphine, chloral hydrate, chloroform and venesection are not employed and delivery is effected only after the cervix has become dilated. Lichtenstein, depending principally on massive venesection (1000 cc.), has reported a maternal mortality of 9.4 per cent. During recent years considerable interest has been aroused by a form of treatment suggested by Lazard, in which 20 cc. of a 10 per cent. solution of magnesium sulphate are injected intravenously every hour until the convulsions cease. In Lazard's most recent publication (November 1933), which reviews 225 cases treated by this drug, a maternal mortality of 13.3 per cent. was reported. Luminal, sodium amytal, pernocton, and other barbiturates have also been tried in eclampsia, but the results thus far do not seem noticeably better than those cited above.

When methods of treatment so different as those just mentioned, give results so similar, it seems logical to suspect that it is the one feature common to them all, namely, non-interference, which is to be credited with the beneficial results. As noted by DeLee, the sedatives we use in eclampsia have no specific effect in curing the disease, but their value depends on the fact that they stop the convulsions and thus allay the alarm of the attending obstetrician. He is not so readily precipitated into disastrous interference and, feeling that the case is not so threatening, takes his time and lets Nature take her course.

While sedative drugs, particularly morphine, remain the most dependable form of treatment in eclampsia, gratifying results are reported by several authors from other types of therapy. Most noteworthy of these, perhaps, is the intravenous injection of concentrated solutions of glucose. The purpose of this medication is several-fold. In the first place, when administered in high concentrations and during a short period of time, it usually produces diuresis. Since oliguria, approaching anuria, is the rule in eclampsia, this effect is altogether welcome; indeed, if diuresis can once be established in this disease, recovery usually follows promptly. In the opinion of Cushny, Bastedo and other pharmacologists, the diuretic effect of intravenous injections of glucose is due chiefly to the accompanying glycosuria. When large amounts of glucose pass from the blood into the kidney tubules, either in diabetes or after intravenous injections of sugar, the tubular epithelium is unable to take up the excess of sugar and, furthermore, lacks the power to absorb water against the osmotic pressure of this substance. The result is that both water and sugar pass through the tubules and become part of the urine. It appears probable that in eclampsia the diuresis which commonly follows glucose injections may be due, in part at least, to factors other than this glycosuria, since an increased urinary output may follow the administration of glucose in this disease even though little or no sugar appears in the urine. These very hypertonic solutions of glucose, when introduced into the blood stream, abstract water from the tissues and the resultant increase in blood volume undoubtedly plays an important part in the diuretic effect. Thus, Tilney, Kennedy and others find hypertonic solutions of glucose valuable in depleting the cerebrospinal fluid in cases with high intracranial

pressure. Some authors believe that the urinary suppression which occurs in eclampsia is due to spasm of the renal arterioles and explain the diuretic action of glucose on the grounds that it relaxes these vessels. But the salutary effect of glucose in eclampsia is not limited to the diuresis which it usually produces. As the result of the experimental work of Whipple, Mann and others, it is recognized that toxic substances are less likely to cause liver injury if accompanied, or preceded, by a liberal injection of glucose. For instance, the typical liver lesion of chloroform poisoning is more difficult to produce if glucose is administered at the same time as the chloroform. Mann has demonstrated that the liver requires carbohydrates and that large amounts serve both to spare and to activate this organ. Since the characteristic lesion of eclampsia is an hepatic one, the use of glucose in this disorder seems justified on the basis of its "liver-sparing" effect alone. In combating the acidosis which is often encountered in eclampsia, glucose is also of value, and following injections of this easily oxidizable substance, the carbon dioxide combining power of the blood may rise as much as ten volumes per cent. Titus and his associates have found that if serial blood sugar readings be made during an attack of eclampsia, wide fluctuations occur within exceedingly short intervals of time; moreover, the convulsive seizures occur at levels which Titus calls relative hypoglycemia. He feels that the convulsions may be actually the result of this hypoglycemia and employs glucose to raise the blood sugar. Stander and Harrison have attempted to corroborate the findings of Titus by studying the blood sugar at five minute intervals in eight eclamptic patients, but were unsuccessful in duplicating Titus' results. However, it is unnecessary to invoke the hypothesis of Titus to justify the use of glucose in eclampsia, for, as we have seen, its benefits are manifold. On the indication of a persistent anuria, or a blood carbon dioxide combining power of less than thirty volumes per cent., the writer occasionally uses 500 cc. of a 20 per cent. solution of glucose in eclamptic patients, injecting it intravenously within about thirty minutes. He hesitates to employ a larger total quantity because he fears it might overburden the right ventricle. (Most cases of eclampsia probably die of right heart failure.) Very high concentration of glucose, such as 50 per cent., should likewise be avoided since they sometimes cause thrombosis of the vein. It should not be

forgotten, furthermore, that the water used to dissolve the glucose must have been triply distilled in a glass still within forty-eight hours of the time of its use; even with these precautions, severe chills sometimes follow.

Venesection has been used in the treatment of eclampsia for many years. Its beneficial action in certain cases of this disease is probably due to its effect on the heart and circulation rather than to any actual "removal of toxins," as was previously thought. In the presence of beginning heart failure, as evidenced by pulmonary edema, persistent cyanosis and a rapid and irregular pulse, the withdrawal of 500 cc. of blood is sometimes followed by striking improvement. Since cardiac collapse with consequent edema of the lungs is the common mode of death in eclampsia, heart stimulants are being used more and more in this disorder. Several authors recommend the employment of one of the rapidly acting digitalis preparations in all cases of eclampsia in which the pulse rate exceeds 110.

Arnold and Fay have recently advanced a scheme of treating eclampsia based on the principle that the chief end to be sought is dehydration. Drainage of the spinal fluid and the injection of very concentrated solutions of glucose form an important part of their method. Since these authors report only three cases treated in this way, it would be premature to pass judgment on their recommendations, but it may be noted that spinal puncture was tried many years ago in eclampsia with results which were not encouraging.

As one reviews the strenuous therapeutic programs which are sometimes used in eclampsia, one cannot help suspecting that an occasional eclamptic mother dies, not from the disease itself, but from "over-treatment." These patients stand stimulation of all kinds poorly; the introduction of a stomach tube usually causes a convulsion; a venepuncture often does. *Sedatives, darkness and quiet, remain our most dependable allies in treating eclampsia* and should be violated only on strict indication.

The immediate prognosis in a given case of eclampsia is notoriously uncertain. In 1922 Thomas Watts Eden endeavored to ascertain what signs and symptoms are of particularly grave import in this disease and to this end analyzed 547, case records of eclampsia from fifteen London hospitals. As a result of his studies he stated

that there are seven important criteria of severe eclampsia: (1) A temperature over 103° ; (2) A pulse rate over 120; (3) A systolic blood pressure above 200 mm. Hg.; (4) A number of convulsions greater than ten; (5) A urine which becomes solid on boiling; (6) Persistent coma; (7) The *absence* of edema. When a patient exhibited any two of the above phenomena, Eden grouped the case as a severe one; when only one, or none of these phenomena were present, he considered it a "mild" one. The mean mortality in the mild cases was 6.4 per cent., and in the severe ones 33.4 per cent., a ratio of exactly one to five. Using the same criteria, Peckham has analyzed 129 cases of eclampsia, observed at the Johns Hopkins Hospital between 1924 and 1933, and found that the maternal mortality in the mild cases was 2.86 per cent. and in the severe ones 21.05 per cent. By amending these criteria slightly (omitting albuminuria, changing the blood pressure figure to 180 and the number of convulsions to twenty), this author has been able to demonstrate further, as is shown in Table II, that the maternal death rate increases progressively according to the number of the phenomena exhibited. While it is, of course, impossible to set any fixed standards by which the prognosis in eclampsia can be established with precision, the criteria of Eden are often helpful and, at least, permit the obstetrician to differentiate between very mild and very severe cases of this disease.

Positive Criteria	Number of Cases	Maternal Deaths	Mortality Per cent.
0	29	0	0.00
1	73	0	0.00
2	34	3	8.82
3	29	4	13.79
4	25	9	36.00
5	10	5	50.00
6	5	4	80.00

TABLE II. Showing the maternal mortality in eclampsia when the cases are grouped according to certain criteria of severity. (Peckham.)

Our ideas concerning the *remote prognosis* in eclampsia have altered radically during the past ten years. It used to be a commonplace of obstetric teaching that both eclampsia and were rarely followed by permanent damage to the kid-

ally seemed to confer a sort of immunity against subsequent attacks, with the result that the toxemias of late pregnancy were less likely to occur in such patients than in women whose previous pregnancies had been devoid of these complications. Unfortunately, such optimistic views are altogether wrong. In 1924, Harris studied twenty-four cases of eclampsia one year after the attack and found that three patients, or 12.5 per cent., showed definite evidence of chronic nephritis; it appeared probable, moreover, that the nephritis was the direct result of the eclampsia, since neither the past history nor the physical examination showed any other etiological factor. Among fifty-five women who had suffered from preeclamptic toxemia one year previously, the appalling number of thirty-three, or 60 per cent., showed signs of chronic nephritis. Among this latter group, Harris was able to show, moreover, that the length of time the toxic symptoms persisted was an important determining factor in the occurrence of permanent renal damage. These studies of Harris have been confirmed and amplified by many subsequent observers. Young and Syme have found that following eclampsia, 30 per cent. of subsequent pregnancies are toxemic, eclampsia recurring in 5 per cent. of their cases and preeclamptic toxemia in 25 per cent. An analysis by Young, Syme and Crowe of 239 successive cases of eclampsia and albuminuria showed that 20 per cent. of the patients suffered from subsequent impairment of health due to nephritis, hypertension, heart disease and anemia. In conformity with Harris' earlier observations, these authors found that the after-effects of eclampsia and preeclampsia were in large measure dependent on the period over which the patient had been exposed to toxemia, the sequelae being infrequent when this was less than three weeks but very common if it exceeded six weeks. Rucker, in a follow-up study of 113 cases of eclampsia, found that subsequent pregnancies were complicated by eclampsia in 7.5 per cent. of the cases and by some form of late toxemia in from 16 to 27 per cent. Similarly, Peckham, in a study of seventy-four eclamptic women, has shown that 22 per cent. had signs of chronic nephritis several months after delivery; three of his patients had second attacks of eclampsia in subsequent pregnancies. Gibberd, Greenhill, Evans and Strachan, and other authors, have reported similar results in postecclamptic patients.

There is considerable evidence that the underlying pathological

lesion responsible for the late effects of eclampsia, is primarily a vascular one. Thus, Bell has demonstrated that the characteristic glomerular lesion of eclampsia is a marked narrowing of all the capillaries, caused usually by an increase in the thickness of the basement membrane, but sometimes by an increase in the endothelial cells; in one case he was able to identify these characteristic vascular changes in the kidney seven years after the eclamptic attack had occurred. Likewise, Wagener, in a recent study of the arterioles of the retina in the toxemias of pregnancy, has been able to demonstrate a definite relationship between the appearance of the retinal arterioles in the acute hypertensive toxemias of pregnancy and the tendency of the hypertension to persist after the termination of the pregnancy. This author found that in the acute toxemias, organic lesions develop in the arterioles in about 40 per cent. of the cases, often in association with retinitis; in such cases elevation of blood pressure usually persists.

The evidence is, therefore, abundant that chronic nephritis, usually of an arteriolosclerotic character, follows eclampsia in about 20 per cent. of the cases; in the event subsequent pregnancies ensue, a repeated toxemia develops in over 30 per cent. of the cases, while in approximately 5 per cent. eclampsia recurs. In preeclampsia, the remote prognosis is similarly ominous, particularly, if the signs and symptoms of this disorder have persisted for more than two or three weeks.

CHRONIC NEPHRITIS IN PREGNANCY

The condition, "chronic nephritis in pregnancy," has given rise to no little misunderstanding and confusion. Medical clinicians assert that some cases to which obstetricians apply this term are not nephritis at all, since they manifest hypertension only, with no albuminuria, no cast excretion, no red cells in the urine and no diminution of renal function. They point out, moreover, that if we are dealing in certain of these patients with an actual chronic nephritis in which pregnancy has supervened, it seems scarcely justifiable to call the condition a toxemia of pregnancy, since in reality it is an intercurrent disease, just like tuberculosis, or heart disease, or diabetes complicated by gestation.

These criticisms are of more than academic importance and demand explanation if we are to treat these cases intelligently and handle the grave problems they present with assurance. What is this disease entity, "chronic nephritis in pregnancy"?

The clinical characteristics of the condition are plain enough. Before the seventh month of gestation is reached, often during the first half of the process, the patient shows a marked elevation of blood pressure. The hypertension may have existed prior to pregnancy; if so, the early months of gestation bring about an increase both in the systolic and diastolic pressures. Albuminuria and abnormalities of the urinary sediment may be absent; the renal function is often normal; edema is minimal or lacking, and the patient has no complaints other than occasional headaches. But the hypertension persists, usually at a fairly constant level. At this time only one other positive finding may be noted and that is narrowing and tortuosity of the retinal vessels, in other words, a retinal arteriosclerosis. The pregnancy may proceed to the expected date of confinement, or, as commonly occurs, the foetus may die *in utero* and be expelled prematurely. In either event the child is underweight, while the placenta shows an unusual number of infarcts, often red infarcts. Following delivery there may be a slight recession in the blood pressure, but usually it remains indefinitely at a figure only slightly below that observed during pregnancy. Each subsequent pregnancy adds its increment to the hypertension and, as a rule, the exacerbation in the blood pressure occurs earlier and earlier in each succeeding pregnancy. In most of these patients, the hypertension and the arteriosclerosis persist for years without other findings; some show a more malignant course. Sooner or later, however, all manifest certain organic changes. The largest group, probably, show renal alterations: albuminuria and a rather rapid diminution in kidney function. Once the latter sets in, the course is a short one and death ensues, often within a few months, from uremia. Another class of these hypertensive patients, possibly almost as large as the renal group, manifest cardiac changes; hypertrophy, occasional attacks of decompensation and finally fatal heart failure. In a third group, characterized usually by a very marked hypertension, death results from apoplexy.

We have just made note of the fact that patients with chronic nephritis in pregnancy often show normal renal function. Several years ago, Peckham and Stout showed that neither the phenolsulphonphthalein excretion test or the Mosenthal concentration test is of value in differentiating chronic nephritis in pregnancy from the acute toxemias. During a recent five years period, A. L. Dippel and the writer followed from year to year and from pregnancy to pregnancy, forty-eight of these hypertensive women at the Johns Hopkins Hospital and studied their renal function from time to time by means of the blood urea clearance test. The average systolic blood pressure of the group investigated was 193.1 mm. Hg., while the average diastolic was 121.9. Most of these patients had been observed for many years and there can be no doubt that they represented an advanced degree of chronic hypertensive disease. Yet the urea clearance tests of these women, checked by repeated studies at varying intervals, were well within the normal range in over one-third of the group; in only nine patients, or in less than one-fifth, was it markedly diminished (below 50 per cent. of normal). Even in patients who died during the course of the study from uremia, the test was sometimes normal six months before death, while in women who succumbed to heart disease and apoplexy, it tended to be normal even a few weeks before the end.

The normal renal function which is sometimes met in chronic nephritis in pregnancy, becomes understandable when we consider the postmortem findings in these cases. In our series of forty-eight cases just mentioned, there were five autopsy studies. In every one of these fatal cases, the predominant pathological lesion was the same, namely, a generalized arteriolosclerosis. The vessel changes in the spleen, the pancreas and the adrenal were particularly marked, many arterioles showing sclerosis to a degree which resulted in almost complete occlusion. In two cases, in which death had been preceded by uremia, the kidneys showed similar arteriolosclerotic changes, involving the capillary loops, entering arterioles and even the smaller arteries. However, in the three cases in which death was not preceded by uremia, but by cardiac failure (two cases) and apoplexy (one case), the kidneys presented minimal changes, the arteriolosclerotic process being concentrated in other organs. Accordingly, it

seems reasonable to believe that the degree to which renal function is impaired in this condition depends chiefly on the extent to which the progressive vascular process happens to have involved the kidneys. By the same token, these few cases suggest that the condition we call chronic nephritis in pregnancy is primarily a generalized arteriosclerosis, in which the kidneys may or may not be concerned.

Further evidence that the lesion in chronic nephritis in pregnancy is primarily vascular, is afforded by the constancy with which changes in the retinal arterioles are met in this disorder. Mylius, in 1928, demonstrated that in toxemias of pregnancy associated with rise of blood pressure, the primary and most commonly observed lesions of the fundus were spasms and tonic constrictions of the retinal arteries. These occurred both in cases of acute toxemia and in cases in which chronic nephritis had existed previously. The first visible sign is a narrowing of the arterioles of the retina which may affect any or all of the branches of the central artery. This narrowing is often accompanied, or followed, by irregular constrictions of the lumens of the arterioles, usually first or more marked in the smaller nasal branches, which may vary in degree and situation from day to day. In a valuable study of this subject, Wagener has shown that *at some stage of the spastic process permanent sclerotic changes occur in the walls of the arterioles*. Ophthalmoscopically, it is often difficult to determine just when the organic stage sets in. In Wagener's opinion, it is probable that constrictions and irregularities which are still present two weeks after delivery, are sclerotic and no longer simply spastic. Recent histologic studies of the arterioles in sections of peripheral muscle tissue obtained at biopsy suggest that organic changes in the intima occur early in the vasospastic phase of the toxemias and may be present from the onset. The mechanism by which vasospasm causes permanent arteriosclerosis is not altogether clear, but Mylius has suggested that it may be the result of passive congestion in the venous capillary loops secondary to the tonic arterial constrictions.

The findings of these ophthalmologists indicate, then, that during the acute toxemias of pregnancy, spasms of the arterioles develop, which in time, cause permanent changes in the walls of these small vessels. Their findings afford some basis for the observation that

eclampsia and preeclampsia are frequently followed by chronic nephritis. Furthermore, they make plain the fact that the latter condition is part and parcel of the toxemias, so that it might almost be considered a chronic phase of these disorders, which becomes reactivated and aggravated by subsequent pregnancies. Chronic nephritis in pregnancy is, thus, quite other than an intercurrent disease. The cause of the vasospasm is not definitely known, but Hofbauer, Küstner, Anselmino and Hoffmann, and others, have advanced evidence suggesting that the well known vasoconstrictor, posterior pituitary substance, is present in excess amounts in eclampsia and they accordingly believe that this principle may be the cause, not only of the vasospasm, but of the whole clinical picture, as well.

When we turn to the other criticism mentioned above and ask whether the term "chronic nephritis in pregnancy" is a justifiable one for this arteriolosclerotic disease, the answer is more difficult. In considering this question it must be recalled that a vascular disorder of the kidney is essentially a parenchymatous disease of that organ, since the kidney's most important functioning structure, the glomerulus, is itself a bundle of capillaries. While it is true that the generalized arteriolosclerosis may involve organs other than the kidney and frequently to such an extent as to cause death from heart failure and from apoplexy, the evidence indicates that even in these cases conspicuous changes are present in the vascular units of the kidney. In a recent study by McGregor of the histological changes in the renal glomerulus in essential (primary) hypertension, it has been shown that the glomerular lesion in this condition is as typical as the arteriolar lesion. It consists in a decrease in size and a simplification of the glomerulus with a marked thickening and wrinkling of the glomerular basement membrane. In her series of fifty-one cases of essential hypertension, the average percentage of glomeruli so affected in kidneys from the renal group (death from uremia) was forty-seven, in kidneys from the cardiac group (death from myocardial insufficiency or coronary disease) was thirty-three, and in kidneys from the cerebral group (death from apoplexy) was twenty-four. In contrast to this series, McGregor found that kidneys from individuals dying in the fifth, sixth, seventh and eighth decade of life with a history of normal blood pressure, showed 96.2 per cent.

normal glomeruli. She further observed that there are inflammatory glomeruli in any type of essential hypertension but that they are most numerous in the renal group. The lesions are usually focal and as many as 15 per cent. of the glomeruli may be involved. These findings of McGregor, thus, offer some slight basis for the term "chronic nephritis" in these cases. On the other hand, Herrick, who has studied the vascular aspects of the toxemias for many years, feels that "the loose use of the term, 'nephritis,' in association with the toxemias of late pregnancy should no longer be countenanced." He believes that these are simply examples of a vascular disorder and, having much in common with ordinary hypertensive disease, should be so designated. It is the present writer's opinion that clearer thinking might result if some such terms as "Arteriosclerotic Bright's Disease," or "Chronic Hypertensive Disease," or just "Arteriolosclerosis" were applied to this group of cases. It is barely possible that the next few years may see such a change.

By whatever name it is called, the conception of this condition as a vascular disease aids materially in understanding the clinical courses which these cases pursue. For instance, why do they usually become worse about the fifth month of pregnancy? The explanation which is ordinarily given for the exacerbation of chronic nephritis during pregnancy is that the end products of foetal metabolism overtax the excretory power of the maternal kidneys. Since, however, the disease usually becomes worse about the fifth month of pregnancy, it is rather difficult to understand how the catabolic products of the foetus, which weighs at this time scarcely more than a pound, could overburden kidneys which had been handling the end-products of, let us say, 140 pounds of tissue. If we are dealing with an arteriosclerotic process, on the other hand, the circumstance becomes quite comprehensible on the basis of the increase in blood volume and cardiac output which is associated with pregnancy. These changes throw a considerable burden on the vascular system, and it seems something more than a coincidence, in this connection, that they become marked about the fifth month of pregnancy. With these facts at his disposal, the obstetrician will assume a different attitude toward these cases. He will no longer minimize their severity simply because they have no albuminuria, no casts and no diminution of

renal function. Indeed, he will scarcely expect these abnormalities. He will understand that he is dealing with a progressive vascular process and will hesitate to impose on these diseased vessels the 50 per cent. increase in cardiac output which pregnancy entails. He will not permit the continuance of gestation in clear-cut cases of this disorder and will take appropriate steps to prevent subsequent pregnancies. And, in so doing, he will serve the best interests of his patients.

REFERENCES

- ANSELMINO AND HOFFMANN: "The Origin of Nephropathy and Eclampsia Gravidarum from Excessive Function of the Posterior Lobe of the Pituitary," *Arch.f.Gynäk.*, 147:652, 1931.
- BASDEN: "The Value of Cesarean Section in Pre-eclamptic Toxemia," *Brit.M.J.*, 1:58, 1933.
- BELL: "Renal Lesions in the Toxemias of Pregnancy," *Am.J.Path.*, 8:1, 1932.
- BLAND AND BERNSTEIN: "Salt-free Diet in the Treatment of Preeclamptic Toxemia," *Am.J.M.Sc.*, 173:844, 1927.
- DIECKMANN: "The Hepatic Lesion in Eclampsia," *Am.J.Obst.& Gynec.*, 17:454, 1929; 18:757, 1929.
- EASTMAN AND DIPPOL: Unpublished data on urea clearance test in toxemias of pregnancy.
- EDEN: "Prognosis and Treatment of Eclampsia," *J.Obst.& Gynec.Brit.Emp.*, 29:456, 1922.
- HARDING AND VAN WYCK: "Diet in the Treatment of Preeclampsia," *J.Obst.& Gynec.Brit.Emp.*, 33:17, 1926.
- HARRIS: "The After-effects of the Late Toxemias of Pregnancy," *Bull.Johns Hopkins Hosp.*, 35:103, 1924.
- HERRICK: "The Toxemias of Pregnancy and Their End Results from the Viewpoint of Internal Medicine," *Ill.Med.J.*, 62:210, 1932.
- MCGREGOR: "Histological Changes in the Renal Glomeruli in Essential (Primary) Hypertension," *Am.J.Path.*, 6:347, 1930.
- MORTON: "Induction of Labor by Means of Artificial Rupture of Membranes, Castor Oil and Quinine and Nasal Pituitrin," *Am.J.Obst.& Gynec.*, 26:323, 1933.
- PECKHAM: "Chronic Nephritis Following Eclampsia," *Bull.Johns Hopkins Hosp.*, 45:176, 1929.
- PECKHAM AND STOUT: "A Study of the Late Effects of the Toxemias of Pregnancy," *Bull.Johns Hopkins Hosp.*, 49:225, 1931.
- RANDALL: "The Weight Factor in Pregnancy," *Am.J.Obst.& Gynec.*, 9:529, 1925.
- RUPP: "Salt Metabolism in Pregnancy," *Ztschr.f.Geburtsh.u.Gynäk.*, 95:383, 1929.
- SCHWARZ AND DIECKMANN: "Important Procedures in the Conservative Treatment of Eclampsia," *Am.J.Obst.& Gynec.*, 18:515, 1929.
- SIDDAL AND MACK: "Weight Changes in the Last Four Months of Pregnancy," *Am.J.Obst.& Gynec.*, 26:244, 1933.

STANDER: "The Toxemias of Pregnancy," *Medicine*, 8:1, 1920.

STANDER AND PECKHAM: "A Classification of the Toxemias of the Latter Half of Pregnancy," *Am.J.Obst.& Gynec.*, 11:583, 1920.

STEOGANOFF: "On an Improved Prophylactic Method of Treatment in Eclampsia," *Lancet*, 2:62, 1924.

WAGENER: "Arterioles of the Retina in Toxemia of Pregnancy," *J.A.M.A.*, 101: 1380, 1933.

WHITE: "The Effect on the Urinary Output of Water, Chloride, Inorganic Phosphate, Urea, and Ammonia of Varying the Salt and Acid Content of Water Drunk," *Am.J.Physiol.*, 80:82, 1927.

ZANGEMEISTER: "Puerperal Eclampsia," *Deutsche med.Wenschr.*, 47:540, 1921.

IMMUNIZATION AGAINST THE CONTAGIOUS DISEASES OF CHILDHOOD: DIPHTHERIA, SCARLET FEVER, WHOOPING COUGH AND MEASLES*

By LAWSON WILKINS, M.D.

Instructor in Pediatrics, Johns Hopkins University School of Medicine; Visiting Pediatrician, Johns Hopkins Hospital, Baltimore, Maryland

INTRODUCTION

ALTHOUGH immunization against smallpox has been practiced for many years and typhoid fever has been controlled in the armies by vaccination, no progress was made in immunization against the common contagious diseases of childhood until about fifteen years ago. In the past fifteen years the active immunization against diphtheria has been widely employed and its value has become generally recognized. Ten years ago a method for the active immunization against scarlet fever was proposed, and considerable knowledge concerning its advantages and disadvantages has now been accumulated. For fifteen years it has been known that convalescent serum conferred passive immunity against measles. During the last few years promising work has been done suggesting the possibility of immunizing against whooping cough by means of vaccine.

The problem of immunization is somewhat different in each of the diseases mentioned. Likewise it must be considered from a somewhat different viewpoint by the practicing physician, the institutional doctor and the public health official. Some of the immunization methods, as for example, the toxin injection for scarlet fever, have received wide publicity. The mother seeks the advice of the practitioner concerning the protection of her children. He must be familiar with the advantages and shortcomings of each of the methods and must consider the problem both from the standpoint of the needs of the individual child and also from the public health standpoint. The epidemiologist in public health work views the problem of immunization largely from the effect that may be expected upon

* From the Harriet Lane Home of the Johns Hopkins Hospital and the Department of Pediatrics of the Johns Hopkins University.

the morbidity and mortality rates of a disease in a community. He must likewise consider what effect attempts to eradicate a disease will have upon the natural herd immunity of the population in the future.

The present review is written in an attempt to present the present status and the future problems of immunization against diphtheria, scarlet fever, whooping cough and measles.

Diphtheria Immunization

THE HISTORY OF TOXIN-ANTITOXIN

In 1895 Babes and W. H. Park independently observed that diphtheria toxin, when rendered non-toxic by neutralization with antitoxin, still retained its power to cause the production of antitoxin when injected into animals. In 1907 Theobald Smith suggested that it might be possible to employ such toxin-antitoxin mixtures for the production of immunity in man. In 1913 the safety of the procedure was demonstrated by von Behring and shortly afterward the method was employed by Hahn and Sumner during a small epidemic in Magdeburg. However, active immunization against diphtheria probably would never have been widely employed, unless a simple test had been found to determine which individuals are susceptible to infection and to prove the efficiency of immunizing injections. Such a test was made available in 1913 when Schick demonstrated that the intracutaneous injection of 1/50 L. dose of toxin will produce in nonimmune persons a local reaction, while in those immune there is no reaction. Park and Zingher were the first to realize the value of the use of the Schick test and of active immunization with toxin-antitoxin on a large scale. In 1918 they began the serious attempt to immunize the whole child population of New York City, and in the fifteen years following over 500,000 children of that city alone have been given toxin-antitoxin. This pioneer work was quickly followed by others throughout the United States and other countries, so that today millions of children have been actively immunized against diphtheria and the value of the method is thoroughly established.

IMPROVEMENTS IN THE METHOD OF ACTIVE IMMUNIZATION

In the fifteen years since active immunization against diphtheria was first used, a number of improvements and simplifications in the method have been introduced.

Decrease of Toxin-Antitoxin Dose from 3. L. to 0.1 L.—In the beginning toxin-antitoxin mixtures were made by adding antitoxin to the undiluted toxin, so that the original mixtures contained from 3 to 5 L. + doses of toxin per human dose. These mixtures caused quite a severe local reaction in some of the older children. To lessen this, in 1922, the amount of toxin was reduced thirty times to the present 0.1 L. + mixture.

Substitution of Goat or Sheep Serum for Horse Serum.—The antitoxin at first used in toxin-antitoxin mixtures was obtained from immunized horses. Even though the amount of horse serum in the dose injected was very small (0.001 cc. per human dose), evidence was produced^{1, 2, 3, 4} that this would sensitize a considerable proportion of individuals, so that severe serum sickness might follow later therapeutic injections of horse serum. Occasional cases of Arthus' phenomenon were reported after the injection of various antitoxins in persons who had previously been immunized against diphtheria.⁵ Because of the dangers of sensitization, antitoxin prepared from goats or sheep was substituted in the toxin-antitoxin mixtures. Since about 1927 these preparations have been used very extensively instead of the mixture containing horse serum.

Diphtheria Toxoid.—The next improvement in the technic of immunization was the substitution of toxoid for toxin-antitoxin. It has been known for years that when diphtheria toxin is treated with 0.3 to 0.4 per cent. formalin at 39 degrees to 40 degrees C. for three to six weeks, it becomes non-toxic and yet is capable of producing antitoxin when injected into horses. Diphtheria toxin detoxified with formalin is called "toxoid" or "anatoxine." Glenny and Hopkins⁶ found that toxoid was even a better immunizing agent for animals than toxin itself and Ramon⁷ of the Pasteur Institute, in 1923, and Park and Zingher⁸ first applied it to the immunization of humans. It soon became the accepted method of immunization in France and during the past few years it has gradually replaced the use of toxin-antitoxin in this country. The specifications for toxoid

in the United States are as follows: The toxin before detoxification must contain not less than 5 L. + doses per cc. Detoxification must be so complete that five human doses when injected into guinea pigs must cause no signs of early or late diphtheria poisoning. The antigenic efficiency must be such that the initial human dose will immunize 80 per cent. of guinea pigs in six weeks to such a degree that 5 m.l.d.'s of toxin fail to kill in ten days. Park⁹ states that when the toxoid is ready for use the flocculation test should show at least 8 flocculation units per cc. Toxoid was originally given in three injections. However, it has been found that two doses of 1 cc. each at an interval of three to four weeks suffice to produce excellent immunity. The two dose method is now generally employed.

In infants and young children toxoid rarely ever causes any local or general reactions. In adults and children over eight years of age, 20 to 40 per cent. have slight reactions, 10 to 15 per cent. moderate reactions, and 1 to 5 per cent. strong reactions. An intracutaneous test dose of 0.1 cc. of 1/20 diluted toxoid is sometimes given. Some workers prefer to withhold toxoid or to substitute toxin-antitoxin for those individuals who show a positive skin reaction to the test dose. Experience has shown that unduly severe reactions in older children and adults may be avoided if the regular doses are preceded by two preliminary doses of 0.1 and 0.25 cc. at an interval of one week.

Toxoid has five advantages over toxin-antitoxin mixtures as an immunizing agent:

1. It is from 20 to 30 per cent. more effective, even when only two doses are given. Various workers who have retested groups of children after immunization with toxin-antitoxin report that from 62 to 88 per cent. have been rendered Schick-negative. Beckman,¹⁰ compiling the statistics of a number of investigators, finds among 24,018 children treated with toxin-antitoxin an average of 73.5 per cent. successful immunization. With toxoid 92 to 100 per cent. success is reported by different workers. Among 3388 cases collected by Beckman, 96.2 per cent. gave negative Schick tests after toxoid injection.

2. Toxoid contains no serum and cannot sensitize to any animal protein.

3. It is absolutely without local or general reaction in practically

all children under seven years of age. Reactions in older children and adults are not dangerous and can largely be avoided by proper precautions.

4. Toxoid is more stable, remains effective for at least eighteen months, and never becomes toxic. Toxin-antitoxin may deteriorate in six months or less. Freezing may cause it to become more toxic.

5. The fact that only two doses of toxoid need be given is a great advantage especially in public health work.

Percutaneous Method of Löwenstein.—To obviate the parents' objection to the use of the needle, Löwenstein¹¹ has attempted immunization by means of inunctions. He believes that, in order to secure absolute immunity, antibacillary as well as antitoxic action must be obtained. Accordingly, he employs an ointment containing both toxoid and unfiltered culture of dead diphtheria bacilli in a lanolin base. The ointment is rubbed into the skin three to five times at intervals of one week. Park and Schroder⁹ and Abt and Feingold¹² have used the method in this country. So far the reports indicate that immunization is obtained in about 70 per cent. of the cases. Apparently the only advantage would be in cases where the mother objects to the use of the needle and in institutions where a nurse can apply it to the children as they enter.

Immunization by Means of Single Injections of Alum Toxoid.—Recent work indicates that immunity against diphtheria may be produced by a single injection of precipitated toxoid. Glenny and Barr¹³ and Wells, Graham and Havens¹⁴ have studied the precipitation of diphtheria toxoid with aluminum potassium sulphate. To the toxoid prepared in the usual manner, by detoxification with formaldehyde, alum was added until no further precipitation occurred. The coarse flocculent precipitate was washed with 0.85 per cent. sodium chloride solution and then resuspended in salt solution in such concentration that 1 cc. contained the desired number of flocculating units. The treatment resulted in a purified product, as evidenced by the fact that nitrogen determinations showed an average loss of 80 to 85 per cent. of the original protein content. Antigenic tests in guinea pigs indicated that a high degree of immunity is produced, a single injection of 5 units resulting in protection against as much as 450 minimum lethal doses of toxin. Graham, Murphree and Gill¹⁵ injected a single dose of 5-10 units of the alum toxoid preparation

into 185 children known to be strongly Schick-positive and found that the Schick was changed to negative in 92.4 per cent. when they were retested two to six months after injection. Of 613 children, mostly of preschool age, whose original immunity status was not known, 96.6 per cent. were Schick negative after a single injection. They explain the effectiveness of the precipitated toxoid on the basis of its relative insolubility, which causes slow absorption and a prolonged antigenic stimulation, whereas the ordinary soluble toxoid is absorbed and excreted rapidly, giving only a transient stimulus to antitoxin production. During the past year, Warthen and Levin¹⁶ of the Baltimore Health Department have administered a single dose of 1 cc. of alum toxoid to about 500 children. Of 299 children known to have been Schick-positive, 87.6 per cent. were found to be negative on retesting eight weeks later.

Another means of producing a slow absorption of toxoid has been employed by Straus.¹⁷ He gave a single intramuscular injection of a concentrated diphtheria toxoid in a lanolin base. The concentration was such that 1 cc. of the mixture contained 100 flocculating units of toxoid. The dose injected was 0.2 cc. or 0.25 cc., amounting to 20-25 units. As shown by the conversion of a positive Schick test to negative, immunity was established in 99 per cent. of 103 cases within two months after a single injection.

Immunization by the single dose method, either with alum toxoid or with the concentrated toxoid in lanolin, is said to produce no more severe reactions than the present two-dose method of the injection of ordinary toxoid. Reactions are absent in children of preschool age and infrequent and quite mild in older children. The more severe reactions are to be expected in those patients who give positive skin reactions to both Schick and heated control material. The advantages of immunization by means of a single injection are obvious. If the immunity can be shown to be as lasting, a single dose method will doubtless take the place of the present method of toxoid immunization.

DEGREE OF PROTECTION AFFORDED BY DIPHTHERIA IMMUNIZATION

In estimating the value of diphtheria immunization two viewpoints may be considered. The practitioner may ask, "How safe is the immunized individual from infection with diphtheria?" On the

other hand, the public health worker is interested in knowing to what extent wholesale immunization may be depended upon to decrease the diphtheria morbidity and mortality in a community.

It must be remembered that no individual can be considered immunized to diphtheria until the Schick test has become negative. The Schick test should always be made after immunization—usually about six months afterwards. According to the method of immunization employed, a certain percentage of persons will be found still to have positive tests. The immunizing injections should then be repeated, and the patient again retested. Only a very occasional individual may remain persistently Schick-positive. When a person has become negative to the Schick test, the question of the reliability of the test as an index of immunity then arises. There is always a possibility that a falsely negative test may be obtained through faulty technic or the use of defective material. When the test is properly performed the absence of a reaction indicates that the individual has at least $1/50$ unit of antitoxin per cc. of the blood serum. The extensive experience of many workers has shown that diphtheria rarely ever occurs in individuals having negative Schick tests. Dudley¹⁸ surveyed the recorded cases of diphtheria in natural Schick-negative reactors and found that in most instances the patients were merely diphtheria carriers with coincident sore throats without membranes. However, it cannot be denied that diphtheria occasionally occurs in a Schick-negative individual after immunization. Blum¹⁹ reports that two out of 198 persons who died from diphtheria in New York City in 1930 had been actively immunized, but he does not state whether their Schick tests had been changed to negative. Immunization even to the point of a negative test cannot be regarded as an absolute guarantee that the individual will not contract diphtheria.

Park and others have shown that after immunization the Schick test has remained negative for six years or longer in 90 to 95 per cent. of the cases. It is commonly believed that in most instances immunity once established will persist throughout life. It is probable that the persistence of the immunity is not due entirely to the original stimulus but is brought about by subsequent repeated exposures to diphtheria carriers.

The ultimate eradication of diphtheria is the final goal of all im-

munization campaigns. The time is probably far distant when it will be possible to immunize every child in the population. It is, therefore, of considerable importance to ascertain how large a portion of the child population must be immunized before the disease can be reduced to negligible proportions. Active immunization was introduced in this country on a wholesale scale during a time when diphtheria was already receding from a period of high epidemicity. It is, therefore, somewhat difficult to measure its effect. However, the results in a number of different communities have been so striking that they shed considerable light on the subject. Godfrey²⁰ has studied the epidemiology of diphtheria in relation to the active immunization of certain age groups. He points out that the immunization of 50 to 70 per cent. of children over five years of age has failed in numerous instances to produce any marked effect on the diphtheria incidence in community. However, the immunization of 30 per cent. or more of the children under five years of age in addition to more than 50 per cent. of children five to nine years has produced an immediate and striking decline in the diphtheria rate of the community as a whole. From the public health standpoint this is the minimum requirement to be attained before a striking reduction can be expected in the morbidity and mortality rates.

SUMMARY

In the past fifteen years the value of active immunization against diphtheria has become generally recognized. Diphtheria toxoid has now largely replaced the use of toxin-antitoxin. Its advantages are higher efficiency in immunization, absence of sensitization to animal serum, greater stability, and fewer doses required. The use of a concentrated toxoid precipitated by alum apparently produces immunity by means of a single injection. Because of its simplicity the single dose method will probably become the method of choice. Löwenstein's ointment is less effective than other methods and would have its use only when there is objection to needle injections.

The Schick test should be performed after immunization. Even when the test has become negative there is always the possibility that infection may occasionally occur. Immunization reduces the risks of infection to a minimum but is not an absolute guarantee.

Epidemiological studies have shown that the immunization of

even a high proportion of school children (50 to 70 per cent.) has failed to affect the morbidity and mortality from diphtheria in the community. However, when 30 per cent. or more of the children under five years of age have been immunized in addition to the older children, diphtheria is reduced to negligible proportions in the entire population.

DIPHTHERIA—REFERENCES

- ¹ HOOKER, S. B.: "Human Hypersensitiveness Induced by Very Small Amounts of Horse Serum," *J.Immunol.*, 9:7, 1924.
- ² GORDON, J. E., AND CRESWELL, S. M.: "To What Extent Do Toxin-antitoxin Mixtures Sensitize to Therapeutic Serum?" *J.Prev.Med.*, 3:21, 1929.
- ³ SPICER, SOPHIE: "The Effect of Previous Administration of Antitoxin and Toxin-Antitoxin on Serum Reaction," *J.A.M.A.*, 90:1778, 1928.
- ⁴ LATHROP, F. L.: "Sensitization to Horse Serum Following Toxin-Antitoxin Injection," *J.A.M.A.*, 89:1602, 1927.
- ⁵ GATEWOOD, W. D., AND BALDRIDGE, C. W.: "Tissue Hypersensitiveness Following the Administration of Toxin-Antitoxin," *J.A.M.A.*, 88:1068, 1927.
- ⁶ GLENNY, A. T., AND HOPKINS, B. E.: "Diphtheria Toxoid as an Immunizing Agent," *Brit.J.Exper.Path.*, 4:283, 1923.
- ⁷ RAMON, G.: "L'Anatoxine diphtérique ses propriétés—ses applications," *Ann. Inst.Pasteur*, 42:959, 1928.
- RAMON, G., AND HÉLIE, G. I.: "Anatoxin as an Immunizing Agent against Diphtheria," *Am.J.Dis.Child.*, 39:685, 1930.
- ⁸ PARK, W. H., AND ZINGHER, A.: "Immunity Results Obtained with Diphtheria Toxoid (Modified Toxin) and 1/10 L + Mixtures of Toxin-Antitoxin in the Public Schools of New York City," *Am.J.Dis.Child.*, 28:464, 1924.
- ⁹ PARK, W. H., AND SCHRODER, M. C.: "Diphtheria Toxin-Antitoxin and Toxoid: A Comparison," *Am.J.Pub.Health*, 22:7, 1932.
- ¹⁰ BECKMAN, H.: "Review of Toxin-Antitoxin and Toxoid in Diphtheria Immunization," *Arch.Pediat.*, 50:211, 1933.
- ¹¹ LÖWENSTEIN, E.: "Neue Ergebnisse der Diphtherieprophylaxe," *München.med. Wchnschr.*, 77:883, 1930.
- ¹² APT, A. F., AND FEINGOLD, B. F.: "Diphtheria Immunization: the Percutaneous Method of Löwenstein," *Am.J.Dis.Child.*, 41:8, 1931.
- ¹³ GLENNY, A. T., AND BARE, M.: "The Precipitation of Diphtheria Toxoid by Potash Alum," *J.Path.& Bact.*, 34:131, 1931.
- ¹⁴ WELLS, D. M., GRAHAM, A. H., AND HAVENS, S. C.: "Diphtheria Toxoid Precipitated with Alum; Its Preparation and Advantages," *Am.J.Pub.Health*, 22:648, 1932.
- ¹⁵ GRAHAM, A. H., MURPHREE, L. R., AND GILL, D. G.: "Diphtheria Immunization with a Single Injection of Precipitated Toxoid," *J.A.M.A.*, 100:1096, 1933.
- ¹⁶ Personal communication—Dr. William H. F. Warthen, Baltimore.
- ¹⁷ STRAUS, H. W.: "Active Immunization against Diphtheria: A Rapid Method with a Single Injection," *J.A.M.A.*, 101:192, 1933.

- "DUDLEY, S. F.: "Control of Diphtheria in Crowded Institutions," *Pub.Health*, 42:48, 1928.
- "BLUM, J.: "Age Factor in Active Immunization of Infants against Diphtheria," *J.A.M.A.*, 98:1027, 1932.
- "GODFREY, E. S.: "Study in the Epidemiology of Diphtheria in Relation to the Active Immunization of Certain Age Groups," *Am.J.Pub.Health*, 22:237, 1932.

In the preparation of this paper, the following articles have also been consulted:

- SCHANBEEG, J. F., AND KOLMER, J. A.: *Acute Infectious Discases*, Chap. XV, "The Prevention of Diphtheria," Lea and Febiger, Philadelphia, 1928.
- GRIFFITH AND MITCHELL: *The Discases of Infants and Children*, Chap. XIV, "Diphtheria," W. B. Saunders Co., Philadelphia, 1933.
- HARRISON, W. T.: "Advantages of Toxoid in Diphtheria Prophylaxis," *Am.J.Pub.Health*, 22:17, 1932.

Scarlet Fever Immunization

The history of scarlet fever immunization is now so familiar that it need only be summarized. Between 1905 and 1907 Savchenko, Gabritschewsky¹, Langovoy², and Nitikin³ carried out extensive work in Russia, demonstrating that streptococci from the throats of scarlet fever patients produce a toxin, and that the injection of a bouillon suspension of killed organisms causes symptoms of scarlet fever. They protected children against the disease by the injection of a vaccine composed of the culture fluid and killed streptococci. Little attention was paid to this work and the streptococcus was not generally accepted as the primary cause of scarlet fever. In 1919 Dochez and Sherman⁴ showed by means of agglutination and protection tests that the hemolytic streptococci of scarlet fever are immunologically specific types. In 1923 G. F. and G. H. Dick⁵ produced the disease experimentally by the inoculation of the throat of volunteers with a culture of scarlet fever streptococcus. The Dicks and others then demonstrated that the scarlatinal streptococcus in culture produces a filterable toxic substance which, when injected into the skin of a susceptible person, causes an area of local erythema in eighteen to twenty-four hours. The same toxic product, if injected in sufficient amounts, is capable of producing the rash, sore throat and other symptoms of the disease. The Dicks⁶ used the intracutaneous injection of toxin to differentiate

susceptible from immune individuals. The method has been generally adopted as the Dick Test and the minimal reacting amount of toxin has been standardized as the "Skin Test Dose" (S.T.D.), Subsequently it was shown by the Dicks⁷ that the subcutaneous injection of repeated doses of toxin causes a positive Dick test to become negative and affords protection against the disease.

There are a number of important points which are still the subject of considerable debate. Of primary importance is the question of the specificity of the scarlatinal streptococci. By means of neutralization tests with convalescent scarlet fever serum or with specific antitoxin, the Dicks⁸ claim that the toxin of scarlet fever streptococci can be sharply differentiated from the toxins of erysipelas and other hemolytic streptococci. However, Toyoda⁹, Wadsworth¹⁰ and Kirkbride and Wheeler¹¹ maintain that it is absolutely impossible to distinguish scarlet fever from other strains of hemolytic streptococci. The recent findings of Trask and Blake¹² demonstrate that scarlet fever may be caused by strains of streptococci differing distinctly in their toxins. In the future the heterogenicity of the scarlatinal streptococci will probably have to be taken into consideration in attempts at immunization.

The second point of dispute concerns the nature of the toxin. It differs from diphtheria and other bacterial toxins in the fact that it is relatively thermostable and is relatively innocuous to laboratory animals. Likewise, newly-born infants fail to show a positive skin reaction to the scarlatinal toxin, even when there is no circulating antitoxin demonstrable in the blood by the Schultz-Charlton and neutralizing tests. These facts have given rise to the hypothesis that the erythema-producing substance is an allergin rather than a true toxin. According to this hypothesis, the young infant is not yet sensitized to the streptococcus and so reacts negatively to the Dick test and would not exhibit the rash of scarlet fever. Through exposure and mild infections with streptococci, sensitization occurs resulting in the appearance of a positive Dick test and a liability to the occurrence of a rash in the event of infection with scarlatinal streptococci. Circulating antibodies are not present at this time. Later, antibodies may appear in the blood due either to repeated mild infections, chronic infections in the tonsils, or an attack of

scarlet fever. The Dick test then becomes negative and the individual is immune to the scarlet fever rash. Bristol¹³, Meyer¹⁴, Stevens and Dochez¹⁵ and Cooke¹⁶ and others give many arguments in favor of this hypothesis. On the other hand, Hooker¹⁷, after reviewing all the arguments, comes to the conclusion that the toxin theory fits the facts better than the allergin theory. It now seems, from the work of Toyoda¹⁸, von Borman and Herholz¹⁹, Ando and Kurauchi²⁰ and others that the difference of opinion may be caused by the fact that the streptococcus filtrate contains two components, a thermolabile substance which is a true exotoxin, and a thermostable substance which acts as an allergin.

It is not necessary for our purpose to discuss the details of the toxic and the allergic theories of scarlet fever as they bear upon the problem of immunization. After all the practical value of the Dick test and of active immunization must be judged by the results obtained in the clinical application of these methods. The questions which must be answered are: (1) How reliable is the Dick test as an index of susceptibility or immunity? (2) To what extent do the present methods of the injection of toxin afford protection against scarlet fever?

THE RELIABILITY OF THE DICK TEST

The foundation stone of all the work on scarlet fever immunization is the Dick test. It is used both to select the susceptible individuals in need of immunization and to determine afterward whether the injection of toxin or its modifications has rendered them immune. It is, therefore, essential to determine how reliable is the test as an index of immunity or susceptibility.

Incidence of Positive Dick Tests According to Age.—Many thousands of Dick tests have been done throughout the world. The variation of the incidence of positive reactions in different age groups is well known. Table I shows the percentage of positive reactions as compiled by Schamberg and Kolmer²¹ from the data of many workers, principally in this country where scarlet fever has not been epidemic, as compared with the percentages found by Toyoda²² in Manchuria and Meršol²³ in Jugoslavia, where the disease was epidemic.

RESULTS OBTAINED BY IMMUNIZATION WITH TOXIN

Much of the early work on immunization is unreliable because either ineffective biologic preparations of the toxin were used or inadequate doses were administered. In some of the earliest work Zingher²⁴ and others gave as little as 800 skin test doses (S.T.D.) divided into three injections. Even when less than 2000 S.T.D. of toxin were administered, the Dick test was changed to negative in 67.5 per cent. of the cases and when the dose was increased to 10,000-25,000 S.T.D. the test became negative in 75 per cent. (Perkins²⁰). However, further investigation showed that on retesting after an interval of some months many of the negative reactors had again become positive. For this reason much larger doses of toxin gradually came to be used. In 1928, Park and Schroder²⁸ were using a total of 26,000-46,000 S.T.D. and found that in 70 to 80 per cent. of cases the Dick test remained negative after six to fifteen months. Since then, however, even larger doses have been used and now the generally accepted procedure in this country is that introduced by the Dicks²⁵ and recommended by the Scarlet Fever Committee. Five doses of 500, 2000, 8,000, 25,000 and 80,000 or 100,000 S.T.D. are administered at intervals of one week. Two weeks after the last dose is given, the Dick test is repeated using 1 S.T.D. on one arm and 2 S.T.D. on the other. If either test is positive a sixth dose of 100,000 S.T.D. is given.

Since Platou³⁰ has compiled ample statistics to show that the smaller doses of toxin formerly used frequently failed to protect against scarlet fever, it is necessary to discard much of the earlier work in judging the protective value of toxin injections. In this present review we shall discuss the more recent work in this country where full doses (100,000 + S.T.D.) were given and we shall consider the very important investigations carried out during the scarlet fever epidemics in Russia, Manchuria and Jugoslavia even though somewhat smaller doses were employed.

Frequency with Which the Dick Test Is Changed to Negative by the Injection of Toxin.—The Dicks²⁵ state that the administration of the full doses of toxin in five injections as now practiced causes the skin test to be entirely negative in 95 per cent. of susceptible persons, within two weeks after the completion of the treatment.

Apparently a sixth dose is all that is required to render the remaining 5 per cent. negative. Whether any individuals are encountered who cannot be made Dick-negative by sufficiently large doses of toxin is not stated. The Dicks insist that, unless the immunization is carried to the point of a negative skin reaction, complete protection against scarlet fever cannot be expected although the severity of a subsequent attack would be modified by the partial immunization.

Results of Immunization during Epidemics.—The most exacting test of immunization is afforded by its use to protect large groups of the population in localities where scarlet fever exists in epidemic proportions. A control is then furnished by a comparison of the morbidity and mortality rates in corresponding age groups of inoculated and uninoculated individuals. The results obtained during a number of the severe scarlet fever epidemics abroad are of special interest in spite of the fact that the large doses of toxin now advocated were not employed. Several small outbreaks in this country are also worthy of note.

In Russia active immunization has been used extensively in combating the widespread epidemics of scarlet fever. Most workers have used combinations of streptococcus vaccine and toxin. Korshun and Spirin³¹ have published their results on the immunization of 61,820 children in Moscow between 1925 and 1928. They compared the results with (1) a "combined vaccine" which afforded a total dose of 1400 to 4700 S.T.D. of toxin according to the age of the child (2) "combined vaccine" followed by one or two more doses of toxin, bringing the total to 2400 to 14,700 S.T.D. and (3) toxin alone in a total dosage of 17,500-22,500 S.T.D. Table III shows the influence of each of these methods on the morbidity from scarlet fever between May 1927 and March 1928. During this period the general scarlet fever morbidity in Moscow remained practically the same as it had been for the three years preceding; namely, 32-34 per thousand among children under seven years of age and 13.4 per thousand among children between seven and eighteen years. Compared to this high general morbidity in Moscow, the morbidity was reduced to 6.1 per thousand by the vaccine, 3.3 per thousand by vaccine and toxin and 0.48 per thousand by the larger doses of toxin alone, when the children in certain kinder-

gartens, schools and other institutions completed full courses of injections.

TABLE III

Comparison of Scarlet Fever Morbidity in Immunized Children with the General Scarlet Fever Morbidity in Moscow, (Korshun and Spirin³¹)

Type of Immunization	Total Children	Number Children under 7 Yrs.	Number Children 7-18 Yrs.	Cases of Scarlet Fever	Morbidity per Thousand of Injected	Morbidity per Thousand in Moscow	
						Under 7 Yrs.	7-18 Yrs.
Vaccine + 1400 - 4700 S.T.D. toxin	1476	?	?	9	6.1		
Vaccine + 2400 - 14,700 S.T.D. toxin	6123	2807	3316	20	3.3	33.0	13.4
Toxin only 17,500 - 22,500 S.T.D.	4161	919	3242	2	0.48		

The striking results achieved by the methods of immunization in reducing the morbidity are apparent. However, the relative values of the three types of immunization are not strictly comparable as a larger proportion of older children, among whom the morbidity is always lower, were treated by the toxin alone. A more accurate estimate of the relative value of vaccine and of toxin is afforded by a comparison of identical age groups carried out in a number of kindergartens and schools as shown in Table IV.

It is apparent from these figures that toxin is at least as efficacious as combined toxin-vaccine. Bessedine³² reported on the results of immunization in Leningrad between 1927 and 1929. The total dose of toxin amounted to 10,000 S.T.D. Among 16,761 children immunized, the scarlet fever rate was 4.5 per thousand as compared with a rate of 37.4 per thousand among 24,730 Dick positive children who were not immunized.

The Manchurian Epidemic.—Between 1924 and 1929, scarlet fever assumed epidemic proportions in Manchuria especially among the Japanese. The results achieved by active immunization with toxin have been reported by Toyoda and his coworkers.²⁶ In 1925-

TABLE IV

Comparison of Results of Immunization with Toxin and with Vaccine + Toxin in Similar Groups, (Korshun and Spirin²¹)

Age Group	Immunization Method	Institutions Immunized	Total Children	Children Susceptible But Not Immunized			Children Immunized		
				Total	Cases of Scarlet Fever	Rate 0/00	Total	Cases of Scarlet Fever	Rate 0/00
4-7 years	Vaccine + toxin (2400-14,700 S.T.D.)	25 kindergartens	1565	653	14	21.4	633	3	4.7
	Toxin only (17,500-22,500 S.T.D.)	25 kindergartens	1419	531	13	24.4	756	1	1.3
7-18 years	Vaccine + toxin (2400-14,700 S.T.D.)	11 schools	4123	1424	12	8.4	1234	2	1.6
	Toxin only (17,500-22,500 S.T.D.)	12 schools	7629	3536	16	4.5	1216	0	0

TABLE V

Effect of Immunization on Scarlet Fever Morbidity—Dairen, Manchuria (Toyoda²⁶)

	Year	Japanese Citizens Exclusive of Primary School Children			Japanese Primary School Children		
		Population	Cases of Scarlet Fever	Attack Rate per 1000	Population	Cases of Scarlet Fever	Attack Rate per 1000
Before immunization..	1925	69,962	191	2.73	8,623	100	11.6
	1926	71,122	629	8.82	8,971	152	16.9
	1927	73,353	317	4.33	9,788	114	11.6
After immunization of primary school children (25,000-40,000 S.T.D.).....	1928	77,455	262	3.38	10,489	41	3.9

1926 immunization was of a very imperfect type, only 5,250 to 15,000 S.T.D. of toxin being injected. The morbidity was only reduced to 16.4 per thousand among the inoculated as compared with 32.4 per thousand among those not immunized. In 1927 the dosage was increased and the Japanese primary school children were given 25,000-40,000 S.T.D. in five divided doses. In 1928, the first year following immunization, the morbidity rate among the primary school population dropped sharply from 11.6 per thousand to 3.9 per thousand in spite of the fact that there was no decrease in the morbidity among the uninoculated population, as shown in Table V.

An interesting comparison of the morbidity rates of inoculated and uninoculated groups of children is furnished by the statistics of Toyoda²⁶ from Dairen and by Ozaki²⁶ from the Japanese school children under the jurisdiction of the South Manchurian Railway Company. This is shown in Table VI.

TABLE VI

Comparison of Morbidity Rates in Inoculated and Uninoculated Groups of Japanese School Children

	Number	Cases of Scarlet Fever	Attack Rate per 1000
<i>Japanese School Children of the S. M. R. Co., (Ozaki²⁶)</i>			
Not Dick tested; not immunized.....	1849	44	23.8
Dick positive; not immunized.....	47	5	106.4
Dick negative; not immunized.....	1495	2	1.3
Dick positive; completely immunized....	1112	3	2.6
<i>Dairen Primary School Children (Toyoda²⁶)</i>			
Not immunized (Dick test not stated)...	864	54	62.5
Completely immunized.....	1907	2	1.0
<i>Total for Both Series</i>			
Not immunized; Dick positive or not tested.....	2760	103	37.3
Completely immunized.....	3019	5	1.6

It is seen from these figures that of 3019 children "completely immunized" with 25,000-40,000 S.T.D. of toxin, 5 or 1.6 per thousand contracted scarlet fever; whereas of 2760 children not im-

munized (exclusive of those known to be Dick negative) 103 or 37.3 per thousand contracted the disease. Toyoda states that after the doses of toxin which he employed for immunization, retesting showed that only 85 per cent. of the persons injected were rendered negative to the ordinary Dick toxin although 100 per cent. were negative to the thermolabile component. Perhaps if still larger immunizing doses had been used to the point of producing entirely negative Dick tests, still better results might have been obtained.

In Yugoslavia.—Meršol²³ reported his experience with the active immunization of children under fifteen years during the scarlet fever epidemic in Skoplje, Yugoslavia, in 1926-1928. The doses of toxin employed were much smaller than those used by Toyoda or those now recommended in this country. During 1926 and the first months of 1927, 6,000 S.T.D. were given in three doses. After this the dose was increased to 13,500 in three injections of 500, 3,000 and 10,000 S.T.D. If the Dick test remained positive after three months a fourth dose of 5,000 S.T.D. was given. Even with the small doses employed, strikingly favorable results were obtained, as shown in Table VII.

TABLE VII

Results of Scarlet Fever Immunization in Skoplje, Yugoslavia (Meršol²³)

	Number	Cases of Scarlet Fever	Deaths	Attack Rate per 1000
Not Dick tested; not immunized.....	8118	104	30	12.8
Dick negative; not immunized.....	2512	2	1	0.8
Immunized incompletely, only 1 or 2 doses.....	1558	8	1	5.0
Immunized with 3 or 4 doses (13,500- 18,500 S.T.D.).....	2812	2	0	0.7

Use of Active Immunization in the Control of Epidemics in the United States.—In this country very few large outbreaks of scarlet fever have occurred. However, the experience of Rhoads³³ in Waterloo, Iowa, is sufficient to demonstrate the value of immunization. Between September 1928 and March 1929 a total of 803 cases of scar-

let fever occurred in this city of 40,000 population. The school children were then tested and active immunization was urged for those having positive Dick tests. Of 1957 children tested, 989 or 50.5 per cent. were found positive. 492 children were immunized and 92 per cent. of these were found negative on retesting. During the ensuing ten-month period, none of the 492 immunized children developed scarlet fever. Likewise, no cases occurred among 968 children found unsusceptible on the original Dick test. During the same period 102 cases of scarlet fever occurred among children not immunized. Eighty-four of these cases were among children not tested or immunized and eighteen among children found susceptible but not immunized. Mention should also be made of the experience of Ball³⁴ in preventing the spread of scarlet fever among the school children in Harrison County, Kentucky and the success of Blatt and Dale³⁵ in controlling an outbreak of scarlet fever in the St. Vincent's Infant and Maternity Hospital of Chicago.

Prevention of Scarlet Fever among Nurses in Contagious Disease Hospitals.—In the absence of large epidemics, in this country the most important evidence for the value of immunization is derived from its use to protect nurses and internes on contagious disease services where they are amply exposed to scarlet fever. In the earlier work when small doses of toxin were used, immunization frequently failed as shown by Platou.³⁰ However, with the injection of the large doses now used, the reports have been uniformly favorable, and no nurses who have been fully immunized prior to beginning service have contracted the disease. Since the average expectancy of scarlet fever among nurses in such institutions is said to be about 7 per cent., the efficacy of the method has been well demonstrated. For the sake of brevity, the reports of Dick,²⁵ Knights,³⁶ Rhoads,³⁷ Peacock,³⁸ Platou³⁰ and Hektoen³⁹ have been summarized in Table VIII.

THE DURATION OF IMMUNITY

Very little information is available on the duration of immunity produced by the injection of toxin. The information yielded by retesting with Dick toxin is not altogether reliable. Indeed, as previously mentioned, it is debatable whether the skin reaction to toxin is constant in some individuals or whether it fluctuates irregu-

TABLE VIII
The Results of Active Immunization in the Protection of Nurses Against Scarlet Fever

Investigator	Dosage	Total in Insit- tution	Results Among Immunized				Controls Under Observation					
			Total Immu- nized	Cases of Scarlet Fever	Period of Observa- tion	Total	Dick Neg- ative	Dick Not Tested	Dick Posi- tive	Dick Posi- tive or Not Tested	Cases of Scarlet Fever	Period of Observa- tion
Dick, ²² 1929.....	500-100,000	?	1101	0	4½ yrs.	?	?	?	?	?	37	4½ yrs.
Knights, ²⁴ 1928....	500-60,000	274	25	0	1 yr.	249	143†	78	28	106	15	1 yr.
Rhodes, ²⁷ 1931....	500-80,000	1280	298	0	3¼ yrs.	982	533	367	82	449	15	3½ yrs.
Peacock et al., ²⁸ 1932	500-100,000	258	38	0	10 mos.	220	213	0	7	7	4	10 mos.
Platon, ²⁹ 1932.....	500-80,000	680	79	0	2 yrs.	601	?	?	?	?	46	6 yrs.
Hickoen, ³⁰ 1934...	?	1130	289	2*	?	841	309	532	?	532	41	?

* The 2 patients reported by Hickoen as contracting scarlet fever were not immunized before entering the contagious service.

† The toxin preparation used by Knights for the Dick test proved to be unreliable. Three nurses with negative tests developed scarlet fever.

larly between positive and negative at different times. Among others, Kiefer⁴⁰ and Knights³⁶ have encountered difficulties in interpreting the retests after immunization. Perhaps the use of a purified thermolabile toxin as suggested by Toyoda¹⁸ would yield more reliable results.

It has already been pointed out, that following immunization with small doses of toxin, the Dick test frequently reverts to positive or doubtful after a few months. Bull⁴¹ retested fifty children eight years after immunization and found 36 per cent. slightly positive. Even though a total immunizing dose of 34,000 S.T.D. had been used, Kiefer⁴⁰ found that 34 per cent. of forty-one children had again become Dick-positive on retesting after two years. In the Moscow epidemic quoted previously, Korshun and Spirin³¹ found a change from negative to positive in 11 per cent. of 529 children retested after seven and a half to nine months. It was principally with the hope of producing a more lasting immunity that the five dose immunization with over 100,000 S.T.D. was advocated by the Dicks and recommended by the Scarlet Fever Committee. The Dicks²⁵ state that retests made at intervals of one, two and three years indicate that 91 to 95 per cent. of those immunized with this large dose to the point of an entirely negative skin reaction retain their immunity. Between 5 per cent. and 9 per cent. slip back and require a second immunization.

Before active immunization can be urged for all children as a general prophylactic measure, much more work must be done to show how long the immunity persists following large doses of toxin. However, the results obtained in the epidemics of Russia, Manchuria and Jugoslavia give evidence that even the moderate doses of toxin employed afforded protection to the great mass of those injected for periods of two years or more, and that the immunization is a most valuable measure in times of epidemics.

SEVERITY OF REACTIONS DURING IMMUNIZATION

The reactions to the injections of scarlet fever toxin have never proved dangerous to life and no serious complications have been recorded. They are sufficiently frequent and severe, however, as to be a drawback to the use of immunization as a general prophylactic measure, although during epidemics or in institutional work they

can be largely ignored. The reactions may be local or general. The local reaction consists of redness, swelling and pain. It occurs in 40 to 85 per cent. of those injected, but varies considerably in degree. At times the arm may be markedly inflamed from shoulder to elbow. The general symptoms, recorded by Peacock³⁵ in order of frequency, are headaches, pains in joints, vomiting, swollen glands, and erythema. The fever is usually below 38 degrees C but may reach 39 degrees; it usually lasts twelve to twenty-four hours only. Generalized reactions occur in 10 to 15 per cent. of the persons injected. In some cases there is a generalized scarlatinal rash, the red bloated face, circumoral pallor, and even the sore throat, strawberry tongue and desquamation of the skin. Toyoda²⁶ has noted that reactions are more severe with a freshly prepared toxin than with one preserved in the laboratory for some time. With a freshly prepared toxin he has recorded the following incidence of reactions among 384 school children:

	First Inoculation 1000 S.T.D.	Second Inoculation 2500 S.T.D.	Third Inoculation 5000 S.T.D.	Fourth Inoculation 7500 S.T.D.
Reactions	%	%	%	%
Vomiting.....	4.7	10.7	6.9	0.5
Fever.....	21.9	29.5	15.3	6.2
General rash.....	7.8	5.4	1.2	0
Diarrhea.....	0.3	1.2	0	0
Itching.....	5.7	3.6	0	0
Red bloated face....	4.2	4.2	2.4	0
Laid up in bed.....	6.5	7.1	1.2	0
Local reaction.....	42.2	40.5	47.8	40.0

The reactions rarely last over twenty-four hours. Rhoads³⁷ states that among 190 nurses immunized, the time lost from duty was 45.5 days—an average of 0.239 days per nurse.

MODIFICATIONS OF TOXIN

The reactions to toxin are of sufficient importance to make the clinician reluctant to use it for the general immunization of children or to cause the parents to refuse to permit the completion of the injections. In order to receive general favor, preventive measures of this nature must be relatively free from discomfort, require a minimum of injections and must be relatively inexpensive. There is,

therefore, a real need for a nontoxic, highly antigenic scarlet fever streptococcus product, which will be no less effective against scarlet fever than the present toxin and yet be more like diphtheria toxoid in its freedom from reactions and in the number of doses required.

Immunization has been attempted by the administration of toxin by other methods than subcutaneous injection. By spraying toxin on the nasal mucosa, Peters and Allison⁴² were able to obtain a negative Dick test in only 36 per cent. of children treated. Cooke⁴³ was unable to alter the skin sensitivity by 2,500,000 S.T.D. of toxin given orally but obtained favorable results following the rectal instillation of highly concentrated toxin. The Dicks⁴⁴ report that large doses of toxin are tolerated when given by mouth and cause no reactions. With a total dose of 8,000,000 S.T.D. only 73 per cent. of individuals are rendered Dick-negative. Martmer⁴⁵ gave five inunctions of an ointment containing streptococcus toxin, but found only 66 per cent. of 155 patients so treated were Dick-negative at the end of six months.

Various modifications of toxin have been employed. As previously mentioned, the combinations of vaccine and toxin as used in Russia³¹ have no advantages and give rise to just as severe reactions as toxin alone. Larson⁴⁶ attempted to minimize the reactions by the use of a ricineolated toxin. For a time this preparation was extensively used. However, the actual dosage employed was small and subsequent observation proved that adequate protection was not afforded.^{30, 25} Following Ramon's demonstration that diphtheria toxin can be detoxified with formalin without losing its antigenic value, a number of investigators have experimented with a similar formalized toxin of scarlet fever. Zoeller,⁴⁷ Sparrow and Celarek,⁴⁸ Smith,⁴⁹ Ramon and Debre,⁵⁰ McMahan,⁵¹ Toyoda,²⁶ Futagi⁵² and Ando and Ozaki⁵³ have all shown that reactions can be minimized by this method although a somewhat smaller percentage of individuals are rendered Dick-negative than by the use of raw toxin. None of these workers, however, used amounts corresponding to the large doses of toxin now employed in this country (110,000 S.T.D.).

Recently, Veldee⁵⁴ has concentrated scarlet fever toxin four-fold and has then detoxified it with formalin. He administered to susceptible individuals in three weekly doses an amount of this preparation which corresponded to 280,000 S.T.D. of raw toxin before

detoxification. By means of a special test on white rabbits,⁵⁵ he estimated that after detoxification with formalin the actual total antigenic value of the amount administered was equivalent to 128,000 S.T.D. of raw toxin although the skin reacting factor had been reduced to 800 S.T.D. This amount of the concentrated toxoid was given in three doses to children under fifteen years of age "without subsequent reactions except local erythema in a majority of children, accompanied by induration in a few and tenderness in a still smaller number and mild systemic symptoms (slight fever, headache) in only an occasional individual." Of the 1168 persons retested with one S.T.D. of control toxin one month after the last injection, 972 or 83.2 per cent. were Dick-negative. Of 494 persons retested again, an average of eight months after the last dose, 87.0 per cent. were negative as compared with 87.3 per cent. on the first retest. In three institutions immunized by this method, no cases of scarlet fever have occurred so far. Much more work must be done before it can be decided whether such preparations of toxoid are as effective as raw toxin in affording protection against scarlet fever.

COMMENT

In the preceding pages, we have reviewed the present state of knowledge concerning the scarlet fever toxin and the Dick test and the use of scarlet fever immunization. The results obtained in countries where scarlet fever has been epidemic demonstrate the efficiency of the present methods in protecting a high percentage of individuals for a period of at least several years. Likewise, adequate protection has been afforded to individuals in institutions where they are especially prone to exposure. Under conditions where the risk of infection is great, one should not hesitate at present to employ the methods of immunization now in use, even though they have certain imperfections and even though the discomfort from reactions may be great.

The question of the advisability of the general immunization of all children against scarlet fever is often asked of both the practitioner and the public health authority. Should scarlet fever immunization be advocated as positively as diphtheria immunization and smallpox vaccination? Unfortunately there are still a number of important gaps in the knowledge concerning immunization with

toxin and a number of drawbacks to its general use which must be enumerated:

1. The problem of most fundamental importance which remains to be definitely solved is the question of whether scarlet fever is due to streptococci producing a uniform toxin or whether there are heterologous strains producing different toxins. The recent work of Trask and Blake¹² and others points to a heterogenicity among the toxins derived from scarlatinal streptococci. Further work must be done on this subject and any toxin used for immunization must afford protection against all strains of streptococci which may be encountered.

2. Another important argument against the general adoption of scarlet fever immunization is the lack of any reliable knowledge on the duration of the protection afforded. According to the data derived from epidemics (where the full doses now advocated were not employed), most individuals were apparently protected for two years—or perhaps longer. It is stated that in 90 to 95 per cent. of individuals immunized with 100,000 S.T.D., the Dick test was negative for at least one to three years. When the risk of infection is great, even a relatively transient protection is advisable. However, before scarlet fever immunization can be urged for children as a general prophylactic measure under ordinary circumstances, one must be assured of a relatively permanent immunity, such as is afforded by diphtheria toxoid. It would be decidedly impractical in most cases to repeat the Dick test and immunization every few years, especially when the injections are accompanied by reactions.

3. A negative Dick test is not an absolute guarantee of immunity to scarlet fever. This may be due to errors in technic (injecting too deeply into the skin) or to faulty material used. However, some workers have found that the skin reactivity of certain individuals varies from time to time. Nevertheless, in the control of epidemics the Dick test has proved of great value; its occasional unreliability should not serve as an argument against the immunization of Dick positive individuals.

4. Some writers question the value of scarlet fever immunization on the grounds that it protects only against the toxic and erythema-producing effects of the scarlatinal streptococci but does not protect against infection with these organisms. A person who has been

immunized with toxin may still contract throat infections with scarlatinal streptococci and have *scarlatina sine exanthemate* and perhaps even such complications as nephritis. However, the results obtained in controlling epidemics do not indicate that this is an important objection to immunization with toxin.

5. From the practical standpoint, a most important drawback to the general employment of scarlet fever immunization is the frequent occurrence of rather disagreeable reactions. In institutions or in the presence of epidemics they can be ignored. It cannot be denied, however, that the occurrence of unpleasant reactions makes the physician hesitate to urge the immunization of all the children he attends. It is to be hoped that an effective toxoid or some other immunizing substance will be developed which is free from unpleasant effects and requires a smaller number of injections.

SUMMARY

The present status of scarlet fever immunization may be summarized as follows: The method of immunization with large doses of raw toxin now used has proved effective in controlling epidemics and in protecting individuals in institutions where they are especially liable to exposure. Under these circumstances active immunization should be recommended. However, our knowledge concerning the toxin and the immunization is still far from complete. It is entirely possible that certain strains of scarlatinal streptococci may be encountered against which the toxin as now prepared offers no protection. There is as yet no positive knowledge that the immunity conferred lasts more than a few years. A negative Dick test is a fairly accurate, but not positive, guarantee of immunity. For these reasons, one hesitates at present to recommend the active immunization of all susceptible children, especially since the injections are frequently accompanied by unpleasant reactions. In this country, most cases encountered are relatively mild, and the mortality is comparatively low. If a premature claim is made that the injection of toxin affords an almost certain and lasting protection against scarlet fever, the method may be brought into disrepute. It now seems probable that further work may eventually justify such a claim and that an effective antigen may be perfected which will cause few disagreeable reactions. The physician will then be in a

position to recommend scarlet fever immunization as enthusiastically as he now does diphtheria immunization.

REFERENCES—SCARLET FEVER

- ¹GABRITSCHESKY, G. N.: "Scarlatina Vaccine and the Question Concerning the Specificity of the Scarlatina Streptococcus," *Russk.Vrach*, 469, 1906.
- ²LANGOVOY, N. I.: "Observations on the Action of Scarlet Fever Vaccine," *Russk.Vrach*, 565, 1906.
- ³NITIKIN, D. V.: "The Streptococcus Vaccine as a Preventive Measure against Scarlet Fever," *Russk.Vrach*, 989, 1907.
- ⁴DOCHEZ, A. R., AND SHERMAN, L.: "Significance of Streptococcus Hemolyticus in Scarlet Fever: Preparation of a Specific Antiscarlatinal Serum by Immunization of Horse to Streptococcus Hemolyticus Scarlatinae," *J.A.M.A.*, 82:542, 1924.
- DOCHEZ, A. R.: "Etiology of Scarlet Fever," *Mecidine*, 4:251, 1925.
- ⁵DICK, G. F., AND DICK, G. H.: "Experimental Scarlet Fever," *J.A.M.A.*, 81:1166, 1923.
- DICK, G. F., AND DICK, G. H.: "The Etiology of Scarlet Fever," *J.A.M.A.*, 82:301, 1924.
- ⁶DICK, G. F., AND DICK, G. H.: "A Skin Test for Susceptibility to Scarlet Fever," *J.A.M.A.*, 82:265, 1924.
- ⁷DICK, G. F., AND DICK, G. H.: "Scarlet Fever Toxin in Preventive Immunization," *J.A.M.A.*, 82:544, 1924.
- DICK, G. F., AND DICK, G. H.: "Results with the Skin Test for Susceptibility to Scarlet Fever: Preventive Immunization with Scarlet Fever Toxin," *J.A.M.A.*, 84:1477, 1925.
- ⁸DICK, G. F., AND DICK, G. H.: "Specificity of Soluble Toxins Produced by Hemolytic Streptococci," *J.A.M.A.*, 93:1784, 1929.
- ⁹TOYODA, T., MORIWAKI, J., FUTAGI, Y., AND HOSHIZAKI, S.: "Study on the Specificity of the Hemolytic Streptococci Associated with Scarlet Fever," *Brit.J.Dis.Child.*, 27:282, 1930.
- TOYODA, T., MORIWAKI, J., FUTAGI, Y., AND HOSHIZAKI, S.: "Is the Hemolytic Streptococcus Acceptable Epidemiologically as the Etiological Agent of Scarlet Fever?" *Brit.J.Dis.Child.*, 28:89, 1931.
- ¹⁰WADSWORTH, A. B.: "The Hemolytic Streptococci and Antistreptococcus Serum in Scarlet Fever," *Am.J.Pub.Health*, 18:1287, 1929.
- ¹¹KIRKBRIDE, M. B., AND WHEELER, M. W.: "Further Observations on the Toxins of Hemolytic Streptococci," *J.Immunol.*, 13:19, 1927.
- ¹²TRASK, J. D., AND BLAKE, F. G.: "Heterologous Scarlet Fever," *J.A.M.A.*, 101:753, 1933.
- ¹³BRISTOL, L. D.: "Scarlet Fever as a Reaction of Hypersensitiveness to Streptococcus Protein," *Am.J.M.Sc.*, 166:853, 1923.
- ¹⁴MEYER, S.: "Kritisches zu der Dickschen Scharlachlehre auf Grund Klinischer Beobachtungen und Experimenteller Ergebnisse," *Ztschr.f.Kinderh.*, 43:258, 1927.
- ¹⁵STEVENS, F. A., AND DOCHEZ, A. R.: "The Relation of Allergy to Scarlet Fever," *New York State J.Med.*, 29:22, 1929.

- ¹⁰COOKE, J. V.: "The Anaphylactic Factor in Scarlet Fever," *Am.J.Dis.Child.*, 35:991, 1928.
- ¹¹HOOKE, S. B.: "Studies of Scarlet Fever: I. The Allergic Versus the Toxin-Antitoxin Hypothesis," *J.Immunol.*, 24:65, 1933.
- ¹²TOYODA, T., AND FUTAGI, Y.: "Defect of the Dick Test and Its Remedy," *J.Infect.Dis.*, 46:196, 1930.
- Ibid.*: "The Development of Scarlet Fever Rash and of the Positive Skin Reaction," *Am.J.Dis.Child.*, 40:1024, 1930.
- ¹³VON BORMAN, F., AND HERHOLZ, G.: "Die Komplexe Natur der Hauttrübung welche nach Intracutaner Injektion von Scharlachstreptokokken-Bouillon-kulturfiltrat Auftritt," *Klin.Wchnschr.*, 11:1108, 1932.
- ¹⁴ANDO, K., KURAUCHI, K., AND NISHIMURA, H.: "The Dick Test and Allergic Skin Reaction to Streptococcus Nucleoprotein," *J.Immunol.*, 17:361, 1929.
- Ibid.*: "On the Dual Nature of the Dick Toxin," *J.Immunol.*, 18:223, 257, 267, 1930.
- Ibid.*: "Studies on the Toxins of Streptococcus Hemolyticus: VI. Heat Stable Scarlatinal Toxin," *J.Immunol.*, 19:99, 1930.
- ¹⁵SCHAMBERG, J. F., AND KOLMER, J. A.: "Acute Infectious Diseases," Chap. VII, 2nd ed., Lea and Febiger, Philadelphia, 1928.
- ¹⁶TOYODA, T., MORIWAKI, J., AND FUTAGI, Y.: "Does the Dick Reaction with Streptococcus Toxin Indicate Susceptibility to Scarlet Fever?" *J.Infect.Dis.*, 46:188, 1930.
- ¹⁷MENDEL, V.: "Resultate der Dick-Probe und der aktiven Immunisierung gegen Scharlach in Skoplje und Umgebung," *Centralbl.f.Bakt.*, 111:227, 1929.
- ¹⁸ZINGHER, A.: "The Dick Test in Normal Persons and in Acute and Convalescent Cases of Scarlet Fever: Immunity Results with Scarlet Fever Toxin," *J.A.M.A.*, 83:432, 1924.
- Ibid.*: "The Dick Test and Active Immunization with Scarlet Fever Toxin," *INTERNATIONAL CLINICS*, Series 34, 3:216, 1924.
- ¹⁹DICK, G. F., AND DICK, G. H.: "The Control of Scarlet Fever," *Am.J.Dis.Child.*, 38:905, 1929.
- ²⁰OZAKI: reported by
- TOYODA, T., MORIWAKI, J., AND FUTAGI, Y.: "Practical Value of Immunization against Scarlet Fever with Streptococcus Toxin," *J.Infect.Dis.*, 46:219, 1930.
- TOYODA, T., MORIWAKI, J., FUTAGI, Y., AND KUROI, C.: "Scarlet Fever, Results of Experimental Research," *Am.J.Dis.Child.*, 41:1009, 1931.
- ²¹COSTE, F., GEORGE, P., AND YUEN-SI-TCHONG: "Sur la Valeur de la Réaction de Dick," *Paris med.*, 77:237, 1930.
- ²²PARK, W. H., AND SCHRODER, M. C.: "Practical Points about Active Immunization against Diphtheria and Scarlet Fever," *Am.J.Pub.Health*, 18:1454, 1928.
- ²³PERKINS, R. G.: "Active Immunization in Scarlet Fever. Summary of Present Status," *J.A.M.A.*, 89:1239, 1927.
- ²⁴PLATOV, E. S.: "Present Status of Scarlet Fever Prevention and Serum Treatment," *Minnesota Med.*, 15:697, 1932.
- ²⁵KOBISHUN, S. W., AND SPIEIN, A. A.: "Versuch einer aktiven Scharlach-immunisierung der Kinder in Moskau," *Klin.Wchnschr.*, 8:726, 1929.

- ³³ BESSEDINE: "Essai d'immunization active contre la scarlatine par la toxine du streptocoque scarlatineux," *Travaux du XI^{me} Congrès de Bacteriologistes et d'Epidémiologistes de l'U.R.S.S.*, 1:31, 1929; quoted in *Monthly Epidemiological Report of the Health Section of the Secretariat, League of Nations*, R.E. 128 and 129, July and August, 1929.
- ³⁴ RHOADS, P. S.: "The Use of the Dick Methods in the Control of a Scarlet Fever Epidemic in Waterloo, Iowa," *J.Iowa M.Soc.*, 21:443, 1931.
- ³⁵ BALL, R. W.: "Scarlet Fever—Observations on Control Methods as Applied in Harrison County," *Kentucky M.J.*, 30:471, 1932.
- ³⁶ BLATT, M. L., AND DALE, M. L.: "The Control of an Outbreak of Scarlet Fever," *J.A.M.A.*, 98:1437, 1932.
- ³⁷ KNIGHTS, E. M.: "Immunization to Scarlet Fever of Providence City Hospital Student Nurses," *J.Lab.and Clin.Med.*, 14:614, 1928-1929.
- ³⁸ RHOADS, P. S.: "Skin Tests and Immunization against Scarlet Fever and Diphtheria," *J.A.M.A.*, 97:153, 1931.
- ³⁹ PEACOCK, S. C., WERNER, M., AND COLWELL, C.: "Scarlet Fever: A Survey of the Personnel of a Children's Hospital, Including Prophylaxis and Comparative Studies of Special Bacteriologic and Serologic Methods," *Am.J.Dis.Child.*, 44:494, 1932.
- ⁴⁰ HEKTOEN, L., AND JOHNSON, C.: "The Prevention of Diphtheria and Scarlet Fever in Nurses," *J.A.M.A.*, 102:41, 1934.
- ⁴¹ KIEFER, G. L.: "The Value of Active Immunization against Scarlet Fever," *J.A.M.A.*, 91:1885, 1928.
- ⁴² BULL, H. G.: "Report on a Group of Fifty Dick-Tested Children Eight Years After Immunization against Scarlet Fever," *J.A.M.A.*, 101:363, 1933.
- ⁴³ PETERS, B. A., AND ALLISON, S. F.: "Intranasal Immunization against Scarlet Fever," *Lancet*, 1:1035, 1929.
- ⁴⁴ COOKE, J. V.: "Enteral Administration of Scarlatinal Filtrate Toxin," *Am.J.Dis.Child.*, 45:54, 1933.
- ⁴⁵ DICK, G. F., AND DICK, G. H.: "Antitoxic Immunity Resulting from Administration of Toxin by Mouth," *J.A.M.A.*, 98:1436, 1932.
- ⁴⁶ MARTMER, E. E.: "Immunization to Scarlet Fever by the Inunction Method," *J.Pediat.*, 1:155, 1932.
- ⁴⁷ LABSON, W. P., HUENEKENS, E. J., AND COLBY, W.: "Immunization against Scarlet Fever with Toxin Detoxified with Sodium Ricinoleate," *J.A.M.A.*, 86:1000, 1926.
- ⁴⁸ ZOELLER, CH.: "Sur la possibilité de préparer une anatoxine streptococcique," *Compt.rend.Soc.de biol.*, 92:244, 1925.
- ⁴⁹ SPARROW, H., AND CELABEK, J.: "Immunisation contre la Scarlatine à l'aide de l'anatoxine scarlatineuse," *Compt.rend.Soc.de biol.*, 97:957, 1927.
- ⁵⁰ SMITH, J.: "The Modification of Scarlatinal Toxin by Formaldehyde," *Brit.J.Exper.Path.*, 9:49, 1928.
- ⁵¹ RAMON, G., AND DEBRÉ, R.: "Essais d'immunisation de l'homme au moyen d'une anatoxine du streptocoque scarlatineux," *Compt.Rend.Acad.d.sc.*, 189: 64, 1929.
- ⁵² McMAHON, H. O.: "Scarlet Fever Toxoid," *Am.J.Dis.Child.*, 39:66, 1930.
- ⁵³ FUTAGI, Y.: "Improvement of the Prophylactic Immunization against Scarlet Fever by Means of Anatoxin after Ramon's Method," *J.Immunol.*, 19:451, 1930.

- ¹³ ANDO, K., AND OZAKI, K.: "Studies on the 'Toxins' of Hemolytic Streptococci: VIII. On the Scarlatinal Anatoxin and Its Immunizing Value," *J. Immunol.*, 19:535, 1930.
- ¹⁴ VELDEE, M. V.: "Antigenic Value of Scarlet Fever Streptococcus Toxin Modified by the Action of Formalin," *J. Med.*, 13:596, 1932-1933.
Ibid.: "Preparation of a Scarlet Fever Streptococcus Toxoid and Its Use in Active Immunization," *Pub. Health Reports*, 48:549, 1933.
- ¹⁵ VELDEE, M. V.: "The Standardization of Scarlet Fever Streptococcus Anti-Toxin: A Method Employing the Ear of the White Rabbit," *Pub. Health Rcp.*, 47:1043, 1933.

(Continued in next issue.)

CUMULATIVE INDEX

(FORTY-FOURTH SERIES—1934)

(The arabic 1 refers to volume I (March, 1934); and arabic 2 refers to volume II (June, 1934); while the other figures denote the page in which the first reference to the subject will be found.)

A

Abdomen

roentgenography

thorium dioxide in 1:255-257

surgery

See also Appendectomy; Bile ducts;
Colon; Gall bladder; Intestines;
Liver; Pancreas; Pelvis; Peritonitis;
Spleen; Stomach

advances in 1932 1:270-307

anesthesia in 1:270-274

local 1:272

intraperitoneal vaccination, experiments
1:279-280

peritonitis, prevention, 1:270-280

phlebitis, thrombosis, and embolism
complications 1:277

postoperative care 1:274-279

postoperative distension, prophylaxis
1:277-303

pulmonary complications 1:275-79

bronchoscopy in 1:276, 277

oxygen therapy and, procedure 1:278-
279

references 1:303-307

route of infection, study 1:277

serum therapy in complications 1:280

thoracic complications 1:274-279

Abnormalities and deformities

acromegaly 1:222

crippled hand from nerve damage, preven-
tion, cases 2:225-235

infantilism, renal, 1:249

leontiasis ossium 1:187

Abscess

subphrenic, postoperative 2:144-145

Accidents

crippled hand from nerve damage, preven-
tion, cases 2:225-235

industrial, estimating disability, cases,
charts 2:206-225

Acromegaly

produced by anterior lobe extracts 1:222

Addison's disease

adrenaltropic hormone of the pituitary in
relation to 1:225-226

cortical hormone therapy 1:226, 228

sodium deficiency during 1:228

Adrenalin

effect on sympathetic nervous system 1:113,
114, 123

Adrenaltropic hormone 1:225-226

Adrenals. See Suprarenals

Albuminuria

hypoproteinaemia and edema caused by
2:2-3

Allergy. See Anaphylaxis and allergy

Amino-acids

in hepatic insufficiency 1:8

Amputation

diagnosis in gangrene of extremities 1:177

Amyl nitrate

antidote for cyanide poisoning 1:265

Anaphylaxis and allergy

insulin hypersensitivity 1:230-232

Anatomy

liver lobule 1:21; illus. 22

Anemia

aplastic, differentiated from purpura hem-
orrhagica 2:193

celine disease and, therapy 1:237-238

hypochromic

comparative therapeutic methods 1:252

effect of oral iron therapy 1:251-252

pregnancy and 1:255

iron therapy 1:250-253

dosage 1:252

indications for 1:252

in pregnancy 1:255, 256

types suitable for 1:251

pernicious

etiology in pregnancy 1:256

gastric juice therapy 1:254-255

liver extract therapy, results 1:253-254
treatment 253-255

pregnancy and puerperium

etiology 1:250

prevention of infantile anemia 1:253

symptoms and therapy 1:255, 256

types of anemia 1:255

Anesthesia

balanced anesthesia 1:273

barbital compounds 1:273-274

carbon dioxide in control of nausea 1:272

carbon dioxide in technic 1:274

cyclopropane 1:270

- Anesthesia (Continued)**
 divinyl 1:270
 ephedrine 1:271
 ether 1:270
 ethylene 1:270
 Gwathmey's oil-ether 1:272-273
 intratracheal intubation, improvements 1:274
 local and regional 1:272-273
 pantocaine 1:271
 premedication 1:273
 procaine hydrochloride 1:271
 progress in 1:271-274
 rectal
 Gwathmey's oil-ether 1:272-273
 spinal 1:270-272
 duration 1:271
 fatalities, cause 1:271
 nausea controlled by carbon dioxide 1:272
 paralytic ileus therapy 1:300-301
 rational use 1:272
- Angina pectoris**
 pathogenesis, from study of heart wounds 1:136-137, 147
 prognosis and care in the aged, case 1:103-104
- Angiomatosis. See Telangiectasia**
- Anoxemia** 25-26
- Antidotes. See poisons and poisoning**
- Aortic valve**
 disease, and cardiac enlargement 1:42
- Apparatus**
 thoracic hammock for chest wall collapse, illus. 2:119
- Appendectomy**
 mortality rate 1:293-295
 paracentral incision, risk 1:294
 postoperative distention, pitressin therapy 1:297
- Appendicitis**
 children
 lead poisoning differentiated, case 1:207-208, 216
 inflammatory types 1:294
 mortality rate
 England 1:294
 operative and non-operative 1:293-295
 obstructive types 1:295
 perforating, incidence 1:294
- Arachnoid**
 anatomical basis of poliomyelitis invasion 2:24
- Arm**
 crippled from nerve damage, prevention, cases 2:230-234
 fracture, estimating disability, cases, charts 2:207-208, 212, 216-224
- Arrhythmia**
 auricular fibrillation in hyperthyroidism 1:242-243
- Arsenic and compounds**
 jaundice therapy 1:262
- Arteries**
 mammary, internal
 wounds differentiated from heart injuries 1:141
 roentgenography
 dangers 1:177-178
- Arteriosclerosis**
 cerebral, senile changes 1:92
 pregnancy and chronic nephritis 2:240-241, 259-264
- Arthritis**
 endocrine origin disputed 1:235
- Artificial pneumothorax. See Pneumothorax, Artificial; Tuberculosis, Pulmonary**
- Ascites**
 symptoms in hepatic insufficiency 1:4
- Atropine**
 effect on vegetative nervous system 1:113, 114, 120
 vagotonia therapy, cases 1:125-128
- Auricular fibrillation. See Arrhythmia**
- Axilla**
 cancer
 metastases from breast 1:163-164, 168
- B**
- Baker, Benjamin M., and Rienhoff, William Francis** 2:167
 Medical and surgical aspects of peptic ulcer 2:167-187
- Balfour, Donald C., and Watson, James R.**
 Advances in abdominal surgery during 1932 1:270-307
- Barbital and derivatives**
 anesthesia 1:273
- Bigger, I. A., and Porter, William B.**
 wounds of the heart 1:132-158
- Bile**
 cholagogues and cholergics 1:262
 cholesterol in 1:24
 salts
 in jaundice 1:36
 physiology 1:23-24
- Bile ducts**
 cancer
 incidence in biliary operations 1:284
 diseases
 cholagogic and cholergic therapy 1:262
 surgery
 epithelial regeneration after 1:285
- Biliary tract**
 diseases
 pancreatitis and 1:289
 surgery
 postoperative distention, pitressin therapy 1:297-298
- Bilirubin**
 etiology of jaundice 1:26-27

- Bilirubin** (*Continued*)
 latent jaundice and 1:37
 physiology 1:21-23
 references 1:18
 van den Bergh's test 1:30-33, 37
- Bladder**
 cysts: uterocoele of supernumerary
 ureter, bilateral nephroses and megal-
 ourters, recovery 1:159-162
- Blood**
 bilirubin 1:21-23
 latent jaundice 1:37
 symptoms in hepatic insufficiency 1:4-5
 van den Bergh's test 1:30-33, 37
 chlorides
 thyrotropic effect 2:89-91
 coagulation
 purpura hemorrhagica symptoms 2:193-
 195, 202-203
 iodine in
 thyrotropic effect 2:91-92
 platelets
 purpura hemorrhagica symptoms 2:191-
 195, 202-203
 potassium
 thyrotropic effect 2:89-91
 proteins
 hypoproteinaemia with edema in gas-
 tro-intestinal disease, cases 2:1-15
 sodium
 normal and in Basedow's disease, table
 2:95-97
 thyrotropic effect 2:89-91
 thyroid hormone in 2:67
- Blood pressure**
 high
 cardiac enlargement and 1:42, 43
 chronic nephritis of pregnancy 2:253-264
 psychic origin 1:62, 73
- Blood sugar**
 hepatic insufficiency and 1:6-7
 hypoglycemia
 conditions associated with 1:290
 epileptic seizures and 1:234
 sleep disturbances 1:234
 surgery of pancreas in 1:289-291
 vagotonia and, case 1:127-128
- Blood vessels**
See also Capillaries
- Bones**
See also Osteitis
 marble, differentiated from lead poisoning
 1:194
 lead poisoning in children
 pathology 1:202-204; autopsy findings
 204-206
 marrow
 regenerative powers in thrombopenia
 2:199, 200-201
 roentgen diagnosis, cases, illus. 1:192-
 195
- Boyce, Frederick F.**
 Presentation of case of melanoma of male
 breast 1:163
 Presentation of case of Paget's disease
 1:162-163
- Brachial plexus**
 injury, preventing disability, cases 2:228-
 231
- Bradycardia.** *See* Heart, bradycardia
- Brain**
 blood supply
 invasion of poliomyelitis and 2:23
 cancer
 metastases from pigmented mole, case
 1:165
 hemorrhage
 telangiectatic origin, cases 2:45-46
 infarction
 question of "end arteries" 2:23
 lead poisoning in children, pathology,
 autopsy findings 1:204-206
 tumor
 lead poisoning in children differentiated,
 case 1:213, 216
- Breast**
 cancer
 age incidence in male and female
 1:166
 dangerous diagnostic methods 1:167
 diagnosis in the male 1:172
 differences in male and female 1:165,
 166-168
 frequency in the male 1:165
 metastases in male and female 1:167
 muscular infiltration, importance of re-
 section 1:169-171
 melanoma of the male breast 1:163-172
 melanocarcinoma: a corrected diagnosis 1:172
 tumor
 malignancy in the male 1:172
- Bright's disease.** *See* Nephritis
- Bronchitis**
 postoperative 1:275-276
- Bronchopneumonia**
 old age, incidence 1:98; charts 99
- C**
- Calcium**
 content, in vagotonia and sympatheticotonia
 1:123
 deficiency, in jaundice 1:285
 metabolism in skeletal disease 1:235
 relation to iodine in goiter 1:229
- Campolon**
 use in exophthalmic goiter 2:98
- Cancer**
 etiology
 malignancy in moles and warts 1:163-
 164, 165
 trauma 1:163-164, 166, 170

- Cancer (Continued)**
 metastases
 cerebral, from mole 1:165
 liver, from the breast 1:168
 lungs, from the breast, cases 1:164-165, 168
 male and female breast, differences 1:167
 peculiar tricks 1:171
 spleen, from breast 1:169
 old age conditions 1:91
- Cantarow, A.**
 Progress in medicine 1:221-269
- Capillaries**
 resistance in purpura hemorrhagica 2:195-196, 203
- Carbohydrates**
 metabolism, references 1:18
- Carbon dioxide**
 nausea of spinal anesthesia controlled by 1:272
- Carbon monoxide**
 poisoning
 methylene blue as antidote 1:264-265
 methylene blue as a synergist 1:264
- Cardiovascular diseases**
 hyperthyroidism in, incidence 1:242
- Carotene**
 thyrogenic liver damage, therapy 2:97
- Celiac disease**
 anemia in, therapy 1:237-238
 blood picture 1:236-237
 mineral metabolism disturbances in 1:236
 symptoms 1:236
 therapy 1:237
- Cerebrospinal fluid**
 pathogenesis of poliomyelitis 2:22, 24-25, 31-33
- Childe, A. E.**
 Roentgen ray diagnosis of lead poisoning in children 1:192-195
- Chlorine**
 blood content. Blood, chlorides
- Cholagogues.** *See* Bile
- Cholecystitis.** *See* Gall bladder, disease
- Cholelithiasis.** *See* Gall bladder, calculi
- Choleretics.** *See* Bile
- Cholesterol**
 determination in jaundice 1:36
 physiology 1:24
- Chromagogue test** 1:12-14, 16
 references 1:18
- Coeliac disease.** *See* Celiac disease
- Cohn, Isidore**
 The crippled hand 2:225-235
- Coitus**
 interruptus, and cardiac pain, case 1:59
- Collins, Vera L. and Weiss, Samuel**
 Role of the vegetative nervous system in gastro-intestinal disease 1:167-181
- Colon**
 dilatation
 etiology, experiments 1:295
 obstruction
 roentgenography in 1:295-296
- Connell, John H.**
 Carcinoma of the male breast, autopsy 1:165, 168, 170, 171
- Contagious diseases**
 immunization in diphtheria, scarlet fever, whooping cough and measles 2:268-300
- Cortical hormone.** *See* Suprarenal preparations
- Crouse, K. E., and Gorham, L. W.**
 Recent advances in the treatment of cardiac and renal edema 1:76-86
- Cushing, H. B.**
 lead poisoning in children 1:189-191
- Cyanides**
 goiter producing principle in plants 1:229
 poisoning
 amyl nitrate as antidote, procedure 1:265
 methylene blue as antidote 1:263-264
 sodium nitrite as antidote 1:265
- Cyclopropane**
 anesthesia 1:270
- D**
- Dextrose**
 eclampsia therapy 2:253-255
 paralytic ileus therapy 1:300
- Diabetes mellitus**
 gangrene. *See* Gangrene, diabetic
 insulin hypersensitiveness in 1:230-232
- Diaphragm**
 route of infection in surgical complications, study 1:277
- Diarrhea**
 nervous, manifestation of vagotonia 1:119; case 1:127-128
- Dick test**
 scarlet fever immunization 2:275-298
- Diet**
 mineral content of diet ash in treatment of edema 1:76-86
 salt free, in preeclampsia 2:245-246
- Diiodotyrosin**
 hyperthyroidism and 1:230
- Diphtheria**
 immunity 2:267-275
 degree of protection afforded 2:271-273
 references 2:274-275
 Schick test 2:267, 272-273
 toxin-antitoxin 2:267-268
 toxoid 268-271
 Löwenstein method 2:270
 single injection method 2:270-71
- Disability**
 crippled hand from nerve damage, prevention 2:225-235
 estimating extent, cases, charts 2:206-225

- Divinyl ether 1:270
- Drugs
 effect on aged 1:60
- Duodenal tube
 diagnosis of gall bladder disease 1:253-250
- Duodenum
 ulcer
 mistaken for vagotonia, case 1:125-120
 surgical therapy 2:133-160, 177-157
 vagotonia and 1:118
- Dwarfism
 renal 1:249-250
- Dysentery
 amoebic
 hypoproteinaemia with edema, case 2: 5-9
 bacillus dysenteriae Shira with hypoproteinaemia and edema, case 2:9-13

E

- Eastman, Nicholson J.
 Toxemias of later pregnancy 2:256-265
- Eck fistula
 symptoms 1:3, 7
- Eclampsia
 See also pregnancy, preeclampsia
 mortality 2:250-252, 256
 pituirrin contraindicated 2:250
 prognosis, immediate and remote 2:255-258
 therapy 2:252-255
 toxemias of pregnancy 2:250-238
- Edema
 Barker and Lashmet diet 1:77-86
 cardiac and renal
 dietary mineral control in 1:76-86
 references 1:86
 dysentery with, cases 2:5-14
 gastro-intestinal disease with generalized edema, cases 2:1-15
 nephritic 2:2-3
 nutritional, cases 2:4-14
 references 2:14-15
 symptom of hepatic insufficiency 1:4
- Eitel, Herman, and Loeser, Arnold
 Anterior lobe of the pituitary gland, the thyroid gland, and the carbohydrate metabolism of the liver 2:60-86
- Electrocardiography
 heart wounds 1:133-139, 147
- Elliott treatment of pelvic inflammations 1:292-293
- Embolism
 poliomyelitis complications 2:25
 pulmonary, postoperative in peptic ulcer 2:146-147, 159-160
- Empyema
 oleothorax therapy in pneumothorax empyemata 2:123

- Encephalitis
 children
 lead poisoning differentiated, cases 1:214-215, 216
 lead poisoning cause of, case 1:204
- Endocrine glands
 interrelationship 1:114
 liver differentiated from 1:2-3
 relation to vegetative nervous system 1:114-115, 129
 role in disturbance of internal organs 1:107-108
- Endocrine therapy
 See also under glands and hormones, as Inulin; *See also* Ovarian therapy; Pituitary preparations; Suprarenal preparations; Thyroid, therapy
 hyperinsulinism and 1:233
- Epistaxis. *See* Nose, hemorrhage
- Ephedrine
 anesthesia 1:271
- Epilepsy
 hyperinsulinism and 1:234
- Epithelium
 biliary, regeneration after surgery 1:285
- Ergotamine
 effect on vegetative nervous system 1:114
- Ergotoxine
 effect on vegetative nervous system 1:114
- Ether
 anesthesia 1:270
- Ethylene
 anesthesia 1:270
- Exophthalmic goiter. *See* Goiter, Exophthalmic
- Eyes
 diagnostic significance in vagotonia 1:119-120, 124
 injuries, estimating disability, chart 2:214
 pregnancy complications. *See* Pregnancy, eyes in 2:240

F

- Fallopian tubes
 inflammation, physiotherapy 1:291-293
- Fatigue
 hepatic insufficiency and 1:11
- Feces
 urobilinogen in jaundice 1:33-34; table 35
- Fiessinger, Noël
 Hepatic insufficiency 1:1-18
- Foot
 fractures, estimating disability, chart 2:213
- Fractures
 industrial, estimating disability, cases, charts, 2:206-225

G

- Galactose
 test in hepatic insufficiency 1:6-7, 14
 tolerance in jaundice 1:36

- Gall bladder
 calculi
 cancer and 1:284
 duodenal intubation 1:259-260
 etiology 1:258-259
 cancer
 occurrence in biliary operations 1:284
 stones in etiology 1:284
 disease
 chologogic and choleretic therapy 1:262
 duodenal intubation in 1:259-260
 surgery
 cholecystostomy in jaundice 1:283-284
- Gangrene
 amputation, diagnosis for 1:177
 arteriosclerotic
 differential diagnosis, case 1:173-177
 pathology 1:176-177
 diabetic
 differential diagnosis 174
 pathology 1:176-177
 roentgenography with thorotrast, illus. 1:179-180
 diagnosis
 differential, case 1:173-181
 roentgenography
 dangers 1:177
 thorotrast in arteriography, illus. 1:178-181
 thermal
 differential diagnosis 1:175
- Gastric juice
 pernicious anemia therapy 1:254-255
 studies in pregnancy and puerperium 1:255
- Gastro-enterostomy
 complications and sequelae
 peptic ulcer operation 2:148-155
 results in peptic ulcer 1:283; 2:138-139, 185-187
- Gastro-intestinal tract
 diseases
 clinical sign in vagotonia 1:116-119
 differentiation of vagotonia and sympathicotonia in 1:123-124
 generalized edema in, cases 2:1-15
 poliomyelitis virus invasion of 2:34-36
 role of the vegetative nervous system 1:107-131
 symptoms in sympathicotonia 1:121-122
 effect of drugs on vegetative nervous system 1:113-115
- Genitals
 anterior pituitary in relation to 2:70-85
- Geriatrics. *See* Old Age
- Glucose. *See* Dextrose
- Glycogen
 liver and muscle content
 effect of anterior pituitary substance 2: 66-86
 guinea pig liver 2:68-69
 thyrotropic effect on 2:89-91
- Goiter
 cabbage diet in 1:229
 cyanide compound in 1:229-230
 etiology 1:228-230
- Goiter, Exophthalmic
 anterior pituitary extracts, effects 1:255; 2:67, 75, 77
 blood in 2:89-92, 95-97
 heart in
 auricular fibrillation 1:242-243
 histological diagnosis 2:93-94
 iodine and calcium in 1:228-229
 metabolism rates 2:92-97
 preoperative therapy 2:93-97
 iodine, refractory cases 2:93-94, 96-97
 vitamin A and carotin 2:97
 References 2:93
 surgery
 indications in relation to thyrogenic liver damage 2:87-98
 postoperative therapy 2:92-93
- Goldbloom, A. Allen, and Held, I. W.
 Indications for surgical treatment of peptic ulcer 2:133-166
- Goldstein, Hyman I.
 Heredofamilial angiomatosis (Telangiectasia) with recurring hemorrhages 2: 43-56
- Goldstein's disease. *See* Telangiectasia
- Gonads
 actions of anterior pituitary secretions on 1:223-224; 2:70-85
- Gonadotropic hormone 1:223-224
- Gonorrhea
 female, Elliott treatment 1:202
- Gorham, L. W., and Crounse, K. E.
 Recent advances in the treatment of cardiac and renal edema 1:76-86
- Growth
 effect of growth hormone of pituitary 1:223
- Gwathmey's oil-ether
 rectal anesthesia 1:272-273
- Gynecology
 physiotherapy 1:291-292
- H
- Hand
 injuries
 crippled from nerve damage, prevention, cases 2:225-235
 estimating disability, charts 2:212, 218
- Harrison, Tinsley R.
 Enlargement of the heart 1:49-56
- Heart
 bradycardia in hypertrophy 1:54-55
 congenital lesions, and enlargement 1:42
 dilatation 1:41
 congestive failure in relation to 1:43-46, 55-56
 increase in work cause of 1:43-44
 injury to heart muscle cause of 1:44-45
 metabolism increased in 1:45-46

Heart (Continued)

- diseases
 - See also* Heart, functional disease; Heart, hypertrophy; Heart, insufficiency; Heart, murmurs
 - hyperthyroidism and, incidence and types 1:240-244
 - psychoses in organic disease 1:65
 - psychotherapeutic methods in organic disease 1:73
 - displacement, vs. enlargement 1:41
 - enlargement 1:39-56
 - diagnosis 1:39-41
 - differential 1:41
 - references 1:50
 - types 1:41-43
 - functional disease 1:57-75
 - bizarre and unusual complaints, case 1:62-63
 - cardiac pain symptom 1:58-60
 - classification 1:57-58, 70-71, 75
 - diagnosis 1:69-70
 - discussion by Dr. Hill 1:70-75
 - etiology, cases 1:63-70
 - anxiety neuroses, case 1:64
 - emotional factors, cases 1:65-69, 72-73, 75
 - sexual maladjustment, cases 1:59-61, 63, 66-69, 72-73
 - mental disorders in 1:74
 - murmurs 1:61-62
 - palpitation and 1:58
 - references 1:70
 - shortness of breath, symptom 1:61
 - symptoms 1:58-63, discussion 71-75
 - vertigo as a symptom, case 1:60-61, 66-69, 72
 - hypertrophy 1:41
 - bradycardia in 1:54-55
 - congestive failure and 1:46-55, 50
 - tachycardia and fatigue in 1:47-54, 55
 - work as a cause 1:46
 - insufficiency
 - dilatation and 1:43-46, 55-56
 - oedema in, dietary mineral control 1:76-79; cases 1:81-84
 - hyperthyroidism not essential cause 1:244
 - incidence in hyperthyroidism 1:241-242
 - senile, charts 1:98, 100-105
 - treatment 1:104-105
 - thyroidectomy beneficial, case 1:245-246
 - murmurs, organic and functional 1:61-62
 - muscle
 - injury and dilatation 1:44-45
 - pain
 - etiology, cases 1:58-60, 72
 - palpitation
 - etiology 1:58
 - vertigo and, cases 1:60-61

Heart (Continued)

- rate
 - See also* Heart, bradycardia; Heart, tachycardia
 - congestive heart failure and 1:47-48
 - muscle fiber thickness in relation to 1:48-52
 - rheumatic disturbances and tonsillectomy 1:239-240
 - roentgenography 1:40-41
 - senile conditions, charts 1:101-103
 - surgery
 - beginnings 1:133-134
 - suture, technique 1:145
 - wounds and injuries 1:143-148
 - tachycardia
 - fatigue and, in hypertrophy 1:47-54, 55
 - taxycardia
 - paroxysmal auricular, emotional factors, case 1:66-69
 - valves
 - senile conditions, charts 1:101-103
 - wounds and injuries 1:132-138
 - absence of pain in muscle wounds compared to angina pectoris pain 1:130-137, 147
 - aspiration of pericardial sac 1:142
 - case reports 1:148-155; table 156
 - differentiated from other chest wounds 1:140-141
 - electrocardiography 1:138-139, 147
 - fatal nature, concept changed 1:132-133, 147
 - muscle, involving coronary arteries 1:134-139
 - pathologic physiology 1:134-139
 - penetrating 1:146; cases 148-155
 - pleural cavity or chest wall 1:140
 - prognosis 1:146-147
 - references 1:155, 157-158
 - roentgenography and fluoroscopy 1:141-142
 - stab wounds 1:134, 146, cases 1:148-155
 - summary 1:147-148
 - surgery
 - anesthetic, choice of 1:143
 - approach, methods 1:148
 - postoperative complications and care 1:145
 - technique 1:143-145
 - surgery, postoperative results 1:147
 - symptoms and diagnosis 1:139-142
 - chest electrodes, value 1:138-139
 - tamponade, diagnosis 1:134-135
 - signs and symptoms 1:139-140
 - treatment 1:142-146
 - preliminary 1:142-143
- Held, I. W., and Goldbloom, A. Allen
 - Indications for surgical treatment of peptic ulcer; methods; postoperative complications and sequelae and their treatment 2:133-166

- Hemophilia**
oral use of ovarian hormones and implan-
tation of ovary 2:51-52
- Hemorrhage**
See also Purpura, hemorrhagica
heredofamilial angiomatosis with 2:43-56
hypoproteinaemia and edema caused by 2:3
jaundice and 1:284-285
- Hepatic insufficiency.** *See* Liver insufficiency
- Hiccough**
complication of gastric operation 2:145, 160
- Hill, Lewis B.**
Discussion of functional heart disease 1:70-75
- Histamine**
effect on vegetative nervous system 1:114
- Hyperinsulinism**
diet in 1:233
endocrine therapy 1:233-234
epilepsy and 1:234
etiology 1:232
hypertrophy of islands of Langerhans and 1:232, 233
pancreatic tumors and 1:232-233
surgery of the pancreas in 1:232-234
symptoms 1:232
- Hypertension.** *See* Blood pressure, high
- Hyperthyroidism.** *See* Thyroid
- Hypochondriasis**
functional heart disease and 1:57, 71
- Hypoglycemia.** *See* Blood sugar
- Hypoproteinaemia.** *See* Blood, proteins
- Hypophysis.** *See* Pituitary body
- I**
- Immunity**
contagious diseases of childhood: diph-
theria, scarlet fever, whooping cough
and measles 2:266-300
- Impotence**
anxiety neuroses and, case 1:50-61
- Industry and occupations**
injuries, estimating disability, cases, charts 2:206-225
- Infantilism**
renal 1:249
- Infection**
vitamin A not anti-infective 1:239
- Injuries.** *See* Accidents; Industry and occupa-
tions; Jurisprudence, Medical
- Iodine**
blood content. *See* Blood, iodine in
- Insulin**
See also Hyperinsulinism
toxicity, symptoms and treatment 1:230-232
- Intestines**
diseases
clinical symptoms in vagotonia 1:118-119
symptoms in sympathicotonia 1:121-122
gaseous distention, roentgenography 1:296-297
- Intestines (Continued)**
obstruction
drainage by catheter 1:303
enterostomy 1:302-303
paralytic ileus. *See* Intestines, paralytic
ileus
roentgenography in 1:295-296
new diagnostic point 1:297
paralytic ileus 1:297-303
dextrose combined with insulin in 1:300
drugs, effects 1:302
hypertonic salt solutions in: 299-300
morphine in 1:293
physostigmine therapy 1:302
pitressin therapy 1:297-298
pituirrin therapy 1:297-298, 301-302
spinal, and splanchnic analgesia 1:300-301
suction syphonage by catheter in 1:293-299
roentgenography
in acute obstruction 1:296-297
- Intratracheal intubation** 1:274
- Iodine**
deficiency. *See* Goiter
- Iodine and compounds**
diiodotyrosin 1:230
- Iron**
therapy, in anemia 1:250-253
- J**
- Jaundice** 1:19-38
anatomy and physiology of the liver 1:21-24
calcium deficiency in 1:285
catarrhal
cholecystostomy 1:283-284
etiology 1:256-258
classification 1:19
definition 1:19
diagnosis
clinical interpretation 1:19-20
van den Bergh's test 1:30-33, 37
diagnosis, differential
bile salts 1:36
biliary cirrhosis 1:37-38
cholesterol determination 1:36
galactose tolerance 1:36
laboratory methods 1:29-33
latent jaundice 1:36-37
urobilinogen in urine and feces 1:33-34;
table 35
van den Bergh's test 1:30-33, 37
etiology 1:20-21
association with continuity of
bile canaliculi 1:25-27
association with discontinuity of
cells lining bile canaliculi 1:27-29
mechanical causes 1:24-29
hemorrhagic tendency in 1:254-255
hemolytic 1:25-26

Jaundice (Continued)

- hepatic insufficiency and, symptoms 1:5-6
 - obstructive 1:27-29
 - cholecystostomy for 1:28-1
 - parenchymal type 1:29
 - pathological interpretation 1:20-21
 - postarsphenamine, therapy 1:262
 - reference 1:38
 - spirochetal, relation to catarrhal 1:237
- Jurisprudence, Medical**
- estimating extent of disability 2:206-225

K

Kidneys

- excision
 - unilateral, renal function after 1:247-249
- function
 - studies 1:240-247
- inflammation. *See* Nephritis; Pyelitis
- insufficiency
 - scille, chart 1:97-98
- pregnancy complications. *See* Pregnancy, kidney complications

L

Lactation

- controlled by pituitary hormone 1:224

Lactogenic hormone 1:224

Lead

- analysis of toys, pencils and furniture 1:190-191
 - body tissue content 1:201
 - metabolism 1:218
- Lead poisoning**
- biochemical aspects 1:196-201
 - children 1:189-220
 - biochemical properties of absorbed lead 1:203
 - bone lesions 1:203-204; autopsy findings 205-206
 - brain lesions; autopsy findings 1:204-206
 - children, cases 1:192-195, 207-215; table 216
 - autopsy findings 1:203-205
 - résumé of results in 15 cases 1:220
 - diagnosis 1:189-190
 - differential 1:194-195; table 1:216
 - roentgen ray, cases, illus. 1:190, 192-195
 - pathology 1:202-206
 - specific lesions 1:203
 - signs and symptoms 1:196
 - source
 - cosmetics used by nursing mothers 1:202
 - pencils, toys, etc. 1:190-191
 - storage of absorbed lead 1:200, 203
 - treatment 1:217-220
 - acute stage 1:217-218
 - basis of 1:201

Lead Poisoning (Continued)

- calcium diet 1:218
- deleading 1:218-220
 - diet in deleading 1:219
 - résumé of 15 cases 1:220
 - storage of lead in bone 1:218
- circulation and storage of lead in body tissues 1:200, 203
- portals of entry 1:193-200
- references
 - pathology 1:206
 - roentgen ray
 - diagnosis 1:195
 - solubilities of lead compounds in water vs. human serum 1:197-198
 - toxicity related to solubility 1:197-198

Leg

- fractures, estimating disability, case, charts 2:206-207, 213, 219, 220

Leontiasis ossium

- differentiated from Paget's disease 1:187

Lipoids

- metabolism in liver insufficiency 1:9

Liver

- acute yellow atrophy and catarrhal jaundice 1:257
- anatomy of the lobule 1:21; illus. 22
- cancer
 - metastases from breast 1:163
- catarrhal jaundice and hepatic conditions 1:256-258
- chlorine, thyrotropic effect 2:89-91
- cirrhosis
 - jaundice in 1:37-38
- endocrine glands differentiated from 1:2-3
- extract
 - pernicious anemia therapy 1:253-254
- fatty degeneration
 - thyrotropic influences 2:89-91
- function tests
 - estimation of urobilinogen in urine 1:34; table 35
 - galactose test 1:6-7, 14, 36
 - rose bengal test 1:12-14, 16
- glycogen
 - anterior pituitary extract and hyperthyroidism 2:66-86
 - guinea pig liver, content 2:68-69
 - thyrotropic effect 2:89-91
- insufficiency 1:1-18
 - amino-acids in 1:8
 - ammonia coefficient, corrected 1:14
 - chromagogue test 1:12-14, 16
 - edema in 1:4
 - evolution 1:2-3, 15-17
 - galactose in urine 1:14
 - grave 1:9, 12
 - jaundice in 1:5-6
 - metabolism of the lipoids 1:9; proteins 1:7-8; sugars 1:6-7
 - methods of study 1:2, 11-15

- Liver** (*Continued*)
- mild, symptoms 1:10-11, 12
 - moderate 1:9-10, 12
 - nervous disturbances in 1:3
 - prognosis 1:16-17
 - ratio of insufficiency of cleavage 1:15
 - references 1:17-18
 - role of reticulo-endothelial system 1:13
 - symptoms 1:1-9
 - syndromes 1:1
 - urea formation in 1:8-9
 - urobilinuria 1:5-6
 - vascular and hematological signs 1:4
 - wasting in 1:3
 - normal, obstructive, and necrotic lobule, illus. 1:22
 - physiology 1:21-24
 - potassium, thyrotropic effect 2:89-91
 - roentgenography
 - thorotrast in 1:260-261, 285-287
 - contraindications and complications 1:261
 - sodium content, thyrotropic effect 2:89-91
 - thyrogenic effects
 - anterior pituitary substance and carbohydrate metabolism 2:66-86
 - operative indications in exophthalmic goiter based on 2:87-93
 - vitamin A therapy 2:97
- Loeser, Arnold, and Eitel, Herman**
- Anterior lobe of pituitary gland, thyroid gland, and carbohydrate metabolism of liver 2:66-86
- Longcope, Warfield T.**
- Generalized edema associated with disease of the gastro-intestinal tract 2:1-15
- Love, William S.**
- So-called functional heart disease 1:57-70; discussion 70-75
- Lovett, Thelma**
- pathogenesis of poliomyelitis, a review 2:16-42
- Lungs**
- cancer
 - collapse, postoperative, peptic ulcer 2:146, 159
 - infarction, postoperative, in peptic ulcer 2:146-147, 160
 - metastases from the breast, cases 1:164-165, 168
 - postoperative complications 1:275-277
 - surgery
 - pneumonotomy in tuberculosis 2:131
 - tuberculosis. *See* Tuberculosis, Pulmonary
- Lymphatic system**
- poliomyelitis invasion via 2:28-33
- M**
- Maes, Urban**
- Differential diagnosis of gangrene 1:173-181
 - Early case of Paget's disease 1:182-188
 - Melanoma in the male breast 1:163-172
- Mammary arteries.** *See* Arteries, mammary
- Marmite**
- therapy of anemia in celiac disease 1:237
- Martin, Lay**
- Jaundice 1:19-33
- Masturbation**
- cardiac pain and, case 1:60
- Matson, Ralph C., and Matson, Ray W.**
- Operative collapse therapy in pulmonary tuberculosis 2:99-132
- Medicine**
- progress in 1:221-269
 - references 1:265-269
- Megacolon.** *See* Colon, dilatation
- Melanoma**
- male breast 1:163-172
- Melanosarcoma**
- male breast 1:172
- Meningitis**
- pathogenesis of poliomyelitis 2:21-22, 31
 - tuberculous
 - lead poisoning differentiated in children, cases 1:214-215, 216
- Mental disorders**
- organic conditions, senile 1:93
 - senile, causes and management 1:92-95
- Mercury**
- poisoning
 - therapy 1:263
- Metabolism**
- anterior pituitary, thyroid, and carbohydrate metabolism 2:66-86
 - calcium and phosphorus in parathyroidism 1:235
 - dilatation of heart and 1:45
 - lead 1:218
 - parallel to calcium 1:203
 - lipoids, in hepatic insufficiency 1:9
 - mineral, disturbances in celiac disease 1:236
 - protein, in hepatic insufficiency 1:7-8
 - references 1:17
 - role of vegetative nervous system in control 1:112-113
 - sugar, in hepatic insufficiency 1:6-7
 - suprarenals, influence on 1:228
- Methylene blue**
- antidote for cyanide and carbon monoxide poisoning 1:263-265
 - synergist not an antidote 1:264
- Minsch, Walter A.**
- action on vegetative nervous system 1:113
- Mitchell, H. S.**
- Lead poisoning in children 1:207-216
- Mitral valve**
- stenosis, and cardiac enlargement 1:42
- Mole**
- malignancy from 1:163-164, 165
- Monoxide poisoning.** *See* Carbon monoxide
- McBride, Earl D.**
- Estimating the extent of disability 2:206-225

- Morphine
paralytic ileus therapy 1:228
- Moses, Henry Monroe
Management of old age conditions 1:57-100
- Muscarine
action on vegetative nervous system 1:113
- Muschat, M.
Uterocoele of supernumerary uterus:
bilateral huge pyonephroses and megalo-
ureters with recovery 1:159-162
- Muscles
pectoralis
infiltration in breast cancer 1:169-171
- Myocarditis
senile, charts 1:100-103
- N
- Narcolepsy. *See* Sleep
- Nasopharynx
poliomyelitis virus invasion of 2:33
- Nembutal
in anesthesia 1:273
- Nephrectomy. *See* Kidneys, excision
- Nephritis
edema in 2:2-3
dietary mineral control 1:77-80; case
1:79-80
pregnancy complications. *See* Pregnancy,
chronic nephritis
senile, chart 1:97
- Nephrosis. *See* Nephritis
- Nerves
injury
crippled hand and arm, prevention,
cases 2:225-235
intercostal
multiple neurectomy in pulmonary tu-
berculosis 2:130
phrenic
neurectomy in pulmonary tuberculosis
2:111-117, 131
vagus. *See* Vagotonia
- Nervous system
poliomyelitis routes of invasion 2:16-33
- Nervous system, Vegetative
anatomy 1:103-111
diseases
clinical signs and symptom complex
1:116-121
mixed types of vagotonia and sym-
pathicotonia 1:124
effect of drugs 1:113-115, 120
endocrine glands, relation to 1:114-115
functions 1:112-113
parasympathetic. *See also* Vagotonia
anatomy 1:109-110
function 1:113
references 1:130-131
role in gastro-intestinal disease 1:107-131
sympathetic. *See also* Sympatheticotonia
anatomy 1:110-111
function 1:112
- Neurasthenia
functional heart
disease and 1:57, 70
- Neuritis
peripheral
lead poisoning in children differentiated,
case 1:203, 216
- Neuroses
functional heart disease and 1:57-75
- Nevi
malignancy from 1:163-164, 165
- Nicotine
effect on vegetative nervous system 1:114
- Nitrites and derivatives
antidotes in cyanide poisoning 2:261
- Nose
hemorrhage, with or without telangiectasia
2:43-53
- O
- Old age
accidents, or operative results 1:90
anatomic changes 1:83-90
care and treatment, principles underlying
1:89
care in health 1:105-106
case studies 1:96-105
conduct changes 1:93
dangerous age 1:105
deferred 1:100
definition 1:87
diseases
angina pectoris, prognosis and care,
case 1:103-104
cardiac insufficiency, charts 1:93, 100-105
treatment 1:104-105
cerebral arteriosclerosis and mental
changes 1:92-95
chronic nephritis, incidence, chart 1:97
malignancy 1:91
myocarditis and valvular disease, charts
1:100-103
nervous system 1:91-93
organic 1:88
management 1:95-96
pneumonia 1:93; charts 99
prostatic enlargement 1:91
pyelitis, acute and chronic 1:93-94
renal insufficiency, chart 1:97-93
slight discomforts 1:96
treatment, use of drugs 1:90
functional changes 1:88-90
management of conditions 1:87-106
mental disorders 1:91-95
causes 1:92-95
management 1:94-95
organic conditions in 1:93-94
onset, beginnings and causes 1:87-88
references 1:106
surgical conditions 1:90-91
- Oleothorax therapy
pulmonary tuberculosis 2:120-129

Operative shock. *See* Surgery, shock

Osler's disease. *See* Telangiectasia

Osteitis

- deformans 1:182-183
 - complications 1:186
 - diagnosis 1:182-184
 - differential 1:187
 - endocrine origin disputed 1:235
 - etiology 1:185-186, 187
 - physical changes in 1:184-185
 - prognosis 1:186

fibrosa

- calcium and phosphorus metabolism in 1:235
- diagnoses, erroneous 1:235
- differentiated from Paget's disease 1:187
- parathyroid tumors and 1:234-235

Ovarian therapy

- hemophilia 2:51-52

P

Paget's disease. *See* Osteitis, deformans

Paint

- lead from, in lead poisoning 1:190-191

Pancreas

abnormalities

- surgical treatment and hypoglycemia 1:289

cancer

- hyperinsulinism in 1:233

excision

- hyperinsulinism in surgical conditions 1:232-233

insufficiency

- diagnosis 1:288

islands of Langerhans

- hyperinsulinism and tumors in 1:232, 233
- tumors and hypoglycemia 1:290-291

rupture

- symptoms 1:287-288

surgery

- advances in 1:287-291
- correction of hypoglycemia 1:289-291

tumors

- hyperinsulinism and 1:232-233
- hypoglycemia and 1:290-291
- hypoglycemia and epilepsy with 1:234

Pancreatitis

acute

- biliary diseases and 1:289
- incidence, etiology, operation 1:288-289
- diagnosis 1:288

Pantocaine

- anesthesia 1:271

Paralytic ileus. *See* Intestines, paralytic ileus

Parathyroid

tumors

- osteitis fibrosa and 1:234-235

Payne, R. L., and Whitehead, R. C.

- Purpura hemorrhagica (thrombocytopenia), an evaluation of our present knowledge 2:183-205

Pectoral muscle. *See* Muscles

Pelvis

inflammation

- Elliott treatment 1:292-293

Peptic ulcer

cancer and

- malignant change in benign ulcer 2:182
- secondary carcinoma, diagnosis 1:231-232

- diagnosis 2:163-171

hemorrhage from

- indications for operation 2:135-137, 179-181

- experimental 1:280-281

- medical results 2:174-175, 181-182

- postoperative complications 2:142-156

adhesions 2:154

- gastric 2:142-144, 148-150, 161-163

- gastrojejunal or gastrocolic fistula 2:153-154

- hiccup 2:145, 160

- jejunal or marginal ulcer 2:151-153, 164, 184, 186

- pulmonary 2:146-147, 159

- recurrence or new ulcer 2:150-151, 164

- subphrenic inflammation, and abscess 2:144

- vicious cycle 2:154

perforated

- indications for operation 2:133-135, 177-178

- postoperative therapy 2:156-165

- recurrence 2:150-151, 164, 175

- references 2:165-166

- surgical therapy 1:282-283; 2:133-166; 175-187

- excision 2:139, 155, 185

- gastroenterostomy 2:138-139, 148-155, 185-187

- gastroduodenostomy 2:140

- gastrojejunostomy 2:185-187

- healing processes 2:142-144

- indications 2:133-137, 177-182

- pylorectomy or partial gastrectomy 2:140, 184

- sleeve resection 2:140

- subtotal gastrectomy 2:141-142, 155-156

- type of operation 2:137-142, 182-187

- therapy, medical and surgical aspects 2:167-187

Peritonitis

postoperative

- prevention 1:279-280

- serum therapy 1:280

postoperative distension

- pitressin therapy 1:297-298

- suction syphonage by catheter 1:298-299

Phlebitis

- postoperative complication 1:277

Phosphorus

- metabolism in skeletal disease 1:235

- Physiotherapy
 pelvic inflammations 1:231-253
- Physostigmine
 effect in paralytic ileus 1:302
- Pilocarpine
 effect on vegetative nervous system 1:113, 114, 120
- Pitressin
 paralytic ileus, prophylaxis 1:297-298
- Pituitary body
 "activator of prolactin" isolated 1:224
 adrenotropic hormone 2:23-26
 anterior lobe
 thyroid, and carbohydrate metabolism of liver in relation to 2:66-66
 relation to endocrine glands 1:222-226
 gonadotropic hormones 1:223-224
 growth hormone
 effect on hypophysectomized rats and puppies 1:222-223
 lactogenic hormone 1:224
 physiology 1:221-226
 progress of modern medicine 1:221-222
 sex glands in relation to 2:70, 85
 thyrotropic hormone 1:224-225
- Pituitary preparations
 anterior pituitary extract
 thermolability of thyrotropic substance 2:83-84
 thyroid, and carbohydrate metabolism of liver 2:66-66
 thyroid conditions and 1:224-225
 thyrotropic hormone, effect on thyroid and liver 2:83-91
 growth hormone
 effect of 1:222-223
 from oxen 1:222-223
 paralytic ileus, prophylaxis 1:297-298, 301-302
- Pituirrin
 contraindicated in toxemias of pregnancy 2:250
 paralytic ileus, prophylaxis 1:297-298, 301-302
- Pleura
 adhesions
 artificial pneumothorax failures due to 2:101-103
 extrapleural pneumolysis in tuberculosis 2:129-130
 intrapleural pneumolysis in tuberculosis 2:103-105, 131
 types in tuberculosis 2:106-107
- Plumbism. *See* Lead poisoning
- Pneumolysis
 intrapleural, in pulmonary tuberculosis 2:103-105, 131
- Pneumonia
 old age, occurrence in 1:98; charts 89
 postoperative, prevention 1:275
- Pneumothorax, Artificial
 operative collapse therapy in tuberculosis 2:100-111, 131
- Poliomyelitis
 diagnosis
 lead poisoning differentiated, case 1:210-212, 216
 embolism and thrombosis in 2:25
 epidemiology 2:35-36
 experimental, pathogenesis 2:16-42
 immunity, serum given intracranially, value 2:32
 inoculation methods
 aseptic meningitis by intranasal injection 2:31
 axis-cylinder contacts 2:20-21
 gastrointestinal 2:31-33
 intranasal 2:33
 intrathecal 2:31
 intravenous 2:27
 perineural lymphatics in relation to 2:30
 paralysis
 lower limbs re route of inoculation 2:21
 pathogenesis 2:16-42
 anatomical basis 2:18-19, 23-25, 28
 sequence of infection 2:19-20
 virus in blood, absence 2:26
 pathology 2:26
 portal of entry
 gastrointestinal tract 2:31-36
 nasopharynx 2:33
 transmission
 axonic, experimental evidence 2:22-23
 blood stream route 2:16, 23-28
 lymphatics 2:23-33
 nerve fiber pathways 2:16, 18-23
 transection of spinal cord and 2:22-23
- Polypeptid intoxication
 cause of icterus gravis 1:3
 in hepatic lesions 1:7
- Portal vein
 Eck fistula, symptoms 1:3, 7
- Porter, William B.
 wounds of the heart 1:132-158
- Potassium
 blood content. *See* Blood, potassium
 chloride, in edema 1:77-86
 content, in vagotonia and sympatheticotonia 1:123
- Poisons and poisoning
 carbon dioxide 1:264-265
 cyanide 1:263-264, 265
 mercury 1:263
- Pregnancy
 anemia in. *See* Anemia, pregnancy and puerperium
 arteriosclerosis in 2:240-241, 259-264, 261-262
 chronic nephritis in 2:258-264
 justifiable name for arteriosclerotic disease 2:262-264
 normal renal function and autopsy findings 2:258, 260-261
 symptoms 2:240-242
 vascular lesions primary 2:253-264

Pregnancy (Continued)

- epistaxis in, cases 2:48
- eyes in
 - retinal arteriosclerosis in toxemias 2:240-241, 259, 261-262
- gastric juice studies 1:255
- kidney complications 2:238-242, 258-264
 - remote prognosis in 2:256-258
- low reserve kidney, symptoms 2:238-240
- pituitary origin of substances in blood and urine 1:223
- preeclampsia 2:237-250
 - diet 2:245-247
 - operative procedures 2:247-250
 - pituitrin contraindicated 2:250
 - symptoms 2:237-238, 242-245
- toxemia 2:236-265
 - age and parity as factors 2:241-242
 - classification 2:236-242
 - references 2:264-265

Prolan

- relation to pituitary "sex" hormones 1:223-224

Prostate

- hypertrophy, care in the aged 1:91

Protein

- diet in preeclampsia 1:247
- hypoproteinaemia with edema in gastro-intestinal disease, cases 2:1-15
- metabolism in hepatic insufficiency 1:7-8
- references 1:17

Psychoneuroses

- functional heart disease and 1:57-70, 71-75

Pulmonary tuberculosis. See Tuberculosis, pulmonary**Purpura**

- hemorrhagica 2:188-205
 - capillary resistance lowered 2:195-196, 203
 - classification 2:189
 - coagulation and clot 2:193-195, 203
 - diagnosis 2:197-199
 - etiology and pathology 2:197
 - platelet count 2:191-195, 202-203
 - references 2:204-205
 - symptoms 2:190-196
 - therapy 2:199-202

Pyelitis

- acute and chronic, senile 1:93-94

Pyonephrosis

- bilateral, with ureterocele of supernumerary ureter and megaloureters with recovery 1:159-162

R**Rabinowitch, I. M.**

- Some of the biochemical aspects of lead poisoning 1:196-201

Raynaud's disease

- diagnosis
 - differentiated from gangrene 1:175

Recklinghausen's disease. See Osteitis, fibrosa**References.**

- abdominal surgery 1:303-307
- anterior lobe of pituitary, thyroid, and carbohydrate metabolism of liver 2:85-86
- diphtheria immunization 2:274-275
- edema, dietary mineral control 1:86
- edema with disease of gastro-intestinal tract 2:14-15
- exophthalmic goiter, with secondary thyrogenic liver damage 2:98
- functional heart disease 1:70
- heart enlargement 1:56
- heart wounds 1:155, 157-158
- hepatic insufficiency 1:17-18
- jaundice 1:38
- lead poisoning
 - pathology in children 1:206
 - roentgen ray diagnosis in children 1:195
- medicine, progress in 1:265-269
- old age conditions, management 1:106
- operative collapse therapy in pulmonary tuberculosis 2:132
- operative shock 2:57-65
- peptic ulcer, indications for surgical treatment 2:165-166
- poliomyelitis pathogenesis 2:36-42
- protein metabolism 1:17
- purpura hemorrhagica 2:204-205
- scarlet fever 2:296-299
- telangiectasia with recurring hemorrhages 2:52-56
- toxemias of later pregnancy 2:264-265
- vegetative nervous system in gastro-intestinal disease 1:130-131

Reflex

- Aschner's, in vagotonia 1:120
- Hering's, in vagotonia 1:120

Regeneration

- biliary epithelium, postoperative 1:235

Rendu-Osler-Weber's disease. See Telangiectasia**Reticulo-endothelial system**

- role in hepatic insufficiency 1:13

Rhea, Lawrence J.

- Pathology of lead poisoning 1:202-206

Rheumatic fever

- heart disease and tonsillectomy 1:239-240

Rickets

- lead poisoning differentiated 1:194
- renal 1:249-250

Rienhoff, William Francis, and Baker, Benjamin M.

- Medical and surgical aspects of peptic ulcer 2:167-187

Roentgen rays

- diagnosis
 - dangers in arteriography 1:177-178
 - intestinal obstruction 1:295-297
 - lead poisoning in children 1:190
 - bone changes 1:192-195

- Röntgen rays (*Continued*)
 peptic ulcer 2:170
 thorotrast in arteriography, illus. 1: 173-181
- Ross bengal test
 hepatic insufficiency test 1:12-14, 16
- Ross, S. G.
 Treatment of lead poisoning 1:217-220
- S
- Sarcoma
 melanosisarcoma in the male breast 1:172
- Scarlet fever
 Dick test 2:275-285
 age incidence of positive reactions, table 2:277-278
 morbidity in relation to, table 2:279
 negative test and immunity 2:279
 reactions at onset and after scarlet fever 2:280-281
 reliability 2:277-285
- epidemiology
 results of immunization in Russia, Manchuria, Jugoslavia, and the U. S. tables 2:283-288
- immunity 2:275-285
 allergic versus toxin theories 2:276-277
 drawbacks to general use 2:293-295
 duration 2:288, 299
 modifications of toxin 2:291-293
 nurses in contagious disease hospitals, table 2:288, 289
 reactions, severity, table 2:290-291
 results with toxin 2:282-288
 references 2:295-299
- Schneider, Erich
 Concerning the broadening of the indications for operation in exophthalmic goiter through recognition of secondary thyreogenic injury to liver 2:87-93
- Scurry
 ascorbic acid and vitamin C 1:238
- Serotherapy
 postoperative abdominal complications 1:280
- Sex
 maladjustments and cardiac symptoms, cases 1:59-61, 63, 66-69, 72-73
- Schick test
 diphtheria immunization 2:267, 272-273
- Shock
 operative 2:57-65
 traumatic
 relation to adrenal secretion 1:227
- Shoulder
 disability from damaged nerves, prevention, cases 2:228-231
- Signs
 Loewi's and von Graefe's signs in vagotonia 1:120
- Sleep
 disturbances
 insulogenic hypoglycemia and 1:234
- Sodium
 blood content. *See* Blood, sodium
- Sodium chloride
 therapy
 Addison's disease 1:228
 edema 1:77-86
 paralytic ileus 1:290-300
- Sodium nitrite
 antidote for cyanide poisoning
- Spinal cord
 blood supply and invasion of poliomyelitis 2:24
- Splanchnoptosis
 vagotonia with complications, cases 1:120-123
- Spleen
 cancer
 metastases from the breast 1:169
 excision
 essential purpura hemorrhagica therapy 2:200-204
 in hepatic insufficiency 1:13
 roentgenography
 thorotrast in 1:260-261, 285-287
- Spru
 celiac disease compared to 1:236, 237
- Stentorrhea. *See* Celiac disease
- Stomach
 cancer
 ulcer and,
 diagnosis 1:281-282
 primary or secondary 2:182
- diseases
 clinical signs in vagotonia 1:117-118
 symptoms in sympathicotonia 1:121-122
- hyperacidity
 vagotonia and 1:123
 vagotonia, visceroptosis and, case 1:126-127
- secretions
 gastric juice in pregnancy and puerperium 1:255
- surgery
 postoperative complications of peptic ulcer 2:142-150
 radical vs. conservative, in peptic ulcer 1:281-282
 type for peptic ulcer 2:137-142, 182-187
- therapy
 gastric juice in pernicious anemia 1:254-255
- ulcer
 cancer and. *See* Stomach, cancer
 etiology, animal experimentation 1:280-281
 surgical therapy 1:282-283
 indications; methods; complications and their treatment 2:133-166, 177-187
 vagotonia and 1:118

- Streptococci**
 scarlet fever immunization 2:275-276
- Suprarenal preparations**
 cortical hormone
 effect on adrenalectomized animals 1:226-227
 physiologic effects and therapeutic value 1:226-228
 therapy in Addison's disease 1:226, 228
 cortical tissue source of antiscorbutic factor 1:238
- Suprarenals**
 effect of ablation of hypophysis 1:225
 excision
 effect of cortical hormone therapy in 1:226-227
 functions 1:227
 influence on inorganic metabolism 1:228
 insufficiency
 relation to shock 1:227
 results of studies 1:226-227
- Surgery, *See also* Abdomen, surgery; Anesthesia; and under organs and diseases**
 shock, operative 2:57-65
- Sympathicotonia**
 clinical signs 1:121-123
 clinical study 1:107-131
 differentiated from vagotonia 1:123
 production of 1:111
 references 1:130-131
 summary 1:129
- T**
- Tachycardia. *See* Heart, tachycardia**
- Telangiectasia**
 heredofamilial angiomatosis with recurring hemorrhages 2:43-56
 diagnosis 2:49-50
 therapy 2:50-52
- Thorax**
 surgery
 See also Tuberculosis, pulmonary
 thoracic hammock to increase wall collapse, illus. 2:119
- Thorotrast**
 hepatosplenography 1:260-261
 roentgenography of liver and spleen 1:285-287
 value in arteriography, illus. 1:178-181
- Thrombo-angitis obliterans**
 differentiated from gangrene 174-175
- Thrombocytopenia. *See* Purpura, hemorrhagica**
- Thrombosis**
 poliomyelitis complications 2:25
 postoperative complication 1:277
- Thyroid**
 anterior pituitary extract, effects 1:224-225
 carbohydrate metabolism of liver and hyperthyroidism 2:66-86
 thyrotropic hormone action 2:88-91
- Thyroid (*Continued*)**
 excision
 effect of anterior pituitary extract in 1:225
 effect of anterior pituitary extract in animal experiments 2:80-83
 hyperthyroidism
 anterior pituitary substance, effect 2:66-86
 diiodotyrosin in 1:230
 heart in 1:240-244
 auricular fibrillation, therapy 1:245
 diagnosis 1:244
 masked 1:243-244
 surgery
 cardiac disease and, results 1:244-246
 tumors
 heart in non-toxic adenomata 1:241
- Thyroid preparations**
 diiodotyrosin 1:230
- Thyrotropic hormone. *See* Pituitary preparations, anterior pituitary**
- Tonsillectomy**
 infections following, incidence 1:240
 rheumatic heart disease and 1:239-240
- Toxemia**
See also Pregnancy, toxemia
- Toxin-antitoxin**
 diphtheria immunization 2:267-268
- Trauma**
See also Accidents; Disability; Heart, wounds and injuries
 etiologic factor in cancer 1:163-164, 166, 170
- Tuberculosis**
 children
 lead poisoning differentiated, case 207, 216
- Tuberculosis, pulmonary**
 artificial pneumothorax 2:100-111, 131
 failures due to pleuritic adhesions 2:101-103
 labile mediastinum complicating, oleothorax 2:124-125
 value 2:131
 complications and sequelae
 adhesions 2:101-103, 106-107
 extrapleural pneumolysis 2:129-130
 intercostal neurectomy 2:130
 intrapleural pneumolysis 2:103-105, 131
 end results in 249 cases, table 2:108-111
 indications and contraindications 2:104-105
 postoperative complications, tables 2:107-108
 selection of cases 2:105-107
 value 2:131
 oleothorax therapy 2:120-129
 end results 2:129
 indications and contraindications 2:121-122
 late complications 2:128-129
 oil replacement 2:127-128
 reactions 2:126-129

Tuberculosis (*Continued*)

- selection of oil 2:122-126
 - testing sensitiveness of pleura 2:125-126
 - withdrawal of oil 2:125
 - phrenic neurectomy 2:111-117, 131
 - complications 2:115-116
 - indications 2:114-115
 - results in 500 operations 2:116-117
 - technic, illus. 2:113-114, 121
 - pneumonotomy 2:131
 - surgical therapy
 - operative collapse therapy 2:122-132
 - references 2:132
 - thoracoplasty, extrapleural 2:117-120, 131
 - complications 2:119-120
 - results, table 2:120
- Tumors. See also Cancer**
- melanoma
 - male breast 1:163-172

U

- Urea**
- formation, in hepatic insufficiency 1:8-9
- Ureters**
- ureterocoele of supernumerary ureter, bilateral pyonephroses and megalourters, with recovery 1:159-162
- Uric acid**
- concentration in blood and urine, studies 1:246-247
- Urinary tract**
- dilatation associated with dwarfism 1:249
- Urine**
- bilirubin 1:23
 - van den Bergh's test 1:33, 37
 - examination
 - pancreatic diseases 1:233
 - lead in 1:201
 - renal function studies 1:246-247
 - urobilin
 - in jaundice 1:33-34; table 35
 - symptoms in hepatic insufficiency 1:5-6
- Urobilinogen**
- analysis of urine and feces in jaundice 1:33-34; table 35
- Urobilinurea. See Urine, urobilin**
- Uterus**
- adnexa
 - inflammations, physiotherapy 1:291-292

V

- Vaccine therapy**
- intraperitoneal vaccination 1:279-280

Vagotonia

- cases 1:125-128
 - clinical study 1:107-131
 - differentiated from sympathicotonia 1:123
 - effect of drugs 1:120
 - production of 1:111
 - reference 1:130-131
 - signs and symptom complex 1:116-120
 - summary 1:128-129
 - ulcer patients with hyperacidity 1:123
 - van den Bergh's test 1:50-53, 37
- Veal, J. Ross**
- Thorotrast in arteriography 1:175-181
- Vegetative nervous system. See Nervous system, Vegetative**
- Vernica**
- malignancy from 1:165
- Vertigo**
- functional heart disease and, cases 1:60-61, 65-69, 72

Vitamins

- A, anti-infective factor disputed 1:239
 - thyrogenic liver damage, therapy 2:97
 - B, marmite in celiac disease 1:237
 - C, ascorbic acid and 1:235
 - commercial exploitation, dangers 1:239
 - distribution and effects 1:238-239
- Vogan**
- use in exophthalmic goiter 2:83

W

Warts

- malignancy from 1:165
- Watson, James R., and Balfour, Donald C.**
- Advances in abdominal surgery in 1932 1:270-307
- Weil's disease. See Jaundice, spirochetal**
- Weis, Samuel, and Collins, Vera L.**
- Role of vegetative nervous system in gastrointestinal disease 1:107-131
- Werthof's disease. See Purpura, hemorrhagica**
- Whitehead, R. C., and Payne, R. L.**
- Purpura hemorrhagica (Thrombocytopenia) 2:188-205
- Whooping cough**
- etiology, table 2:299-300
 - immunity 2:299-300
- Wilkins, Lawson**
- Immunization against contagious diseases of childhood: diphtheria, scarlet fever, whooping cough and measles 2:266-300
- Workmen's compensation and insurance estimating disability, cases, charts 2:206-225**